Ocular Oncology Service

Saint Bartholomew's Hospital
The Royal London Hospital
Moorfields Eye Hospital

The International Society of Ocular Oncology

ISOO MEETING 2009

St John's College, Cambridge, UK

Programme and abstracts

Editor: John Hungerford

Front cover:
Wrought iron gate bearing the arms and crest of St John's College, based on those of Lady Margaret Beaufort, Countess of Richmond and Derby, who founded the college in 1511. Margaret Beaufort was the mother of Henry VII and the grandmother of Henry VIII for whom she was briefly regent when he ascended the throne at the age of seventeen.

The International Society of Ocular Oncology

ISOO MEETING 2009

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The International Society of Ocular Oncology

ISOO MEETING 2009

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International congresses of ocular oncology

Past international congresses

I	1977	**Cambridge** (United Kingdom)
II	1981	**Schwerin** (Former East Germany)
III	1984	**Nyon** (Switzerland)
IV	1987	**Zusdel/Moscow** (USSR)
V	1989	**Essen** (Germany)
VI	1992	**New York** (USA)
VII	1994	**Florence** (Italy)
VIII	1997	**Jerusalem** (Israel)
IX	1999	**Philadelphia** (USA)
X	2001	**Amsterdam** (The Netherlands)

International Society of Ocular Oncology congresses

XI	2003	**Hyderabad** (India)
XII	2005	**Whistler** (Canada)
XIII	2007	**Siena** (Italy)
XIV	2009	**Cambridge** (United Kingdom)

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Clifton Hawley III - Director of Business Services
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General information

Auditorium

All sessions will be held in the Fisher Building in St John's College. The meeting language is English.

Badges

Admission to all conference rooms is restricted to registered delegates wearing their name badge. It is requested that badges are worn during all congress meetings, meals and social events.

Registration

The registration desk will be open at 7.30am each day.

The full registration fee for the clinical meeting includes attendance at the welcome reception at the Fitzwilliam Museum followed by a buffet supper at St John's College; coffee, lunch and tea each day; and access to all conference facilities. Tickets will be in your registration pack for all the other social events that you have requested.

Social events

Tuesday 8th September

6.30pm	Opening ceremony at the Fitzwilliam Museum
8.15pm	Buffet supper in St John's College

Wednesday 9th September

7.30pm	Drinks and dinner at King's College

Thursday 10th September

Evening free to enjoy Cambridge

Friday 11th September

7.15pm Conference dinner at St John's College

There will be a representative from the Cambridge Tourist Office available between 9.30am and 11am each morning from Tuesday to Thursday.

Information for speakers

The speaker preparation room is situated on the first floor of the Fisher Building and is available from 7.30am each day.

The programme is very busy and it is essential that you prepare and load your PowerPoint presentation at least one hour before the commencement of the relevant session. If you are speaking in the first session please load your presentation the day before, if possible. If not, please be sure to be very early on the day.

There will be IT technicians to help you view and load your presentation.

Speakers have three or five minutes. Do please keep strictly within your allocation as defined in the programme. Please stand by the podium when the previous speaker begins his lecture. Only if you keep strictly to your allotted time will there be an adequate opportunity for discussion. For free papers, please remember that the purpose of your presentation is to summarise your aims, methods, results and conclusions as defined in your abstract and not to provide more detail than the delegates can assimilate in a few minutes.

Information for poster presentations

Posters may be displayed during the whole congress but please try to ensure that yours is available to view on the day relevant to your subject. There will be a section allocated to each day of the conference. Your poster may be set up during conference hours from 9am on Tuesday 8th. It must be removed by 10am on Saturday 12th. The conference organisers cannot be responsible for posters that are lost or not collected!

The International Society of Ocular Oncology

ISOO MEETING 2009

President's message

Dear Friends,

Thirty-two years after the first ocular oncology congress, the meeting of our sub-speciality returns to Cambridge, this time as an official meeting of the International Society of Ocular Oncology – ISOO.

The field of ocular oncology is a small one in ophthalmology, but it is the only sub-specialty that deals with diseases that threaten life as well as sight. This may be the reason that ocular oncology attracts to its ranks some of the best ophthalmologists in the world, physicians who deeply care about their patients' well-being.

Our Society is a young one which needs to build a solid group of members from all over the world who will feel part of the exclusive but growing family of ocular oncologists and others who have an interest in our field. Building an active website - which will enable us to maintain contact with our members, to consult each other, to educate specialists, residents and researchers, and even to collect dues - will be a step forward toward better organization of our society. Such a website is currently under construction.

I welcome the participants of the XIV International Ocular Oncology Congress, basic scientists and clinicians, to St John's College in Cambridge. This historical institution is a perfect venue for combining scientific and social events in a traditional educational atmosphere with modern facilities.

I want to thank the organizing committee, headed by Mr. John Hungerford, for all their efforts in planning an excellent scientific and social program, and I wish you all an enjoyable and memorable congress.

Professor Jacob Pe'er
President of the International Society of Ocular Oncology

The International Society of Ocular Oncology

ISOO MEETING 2009

Conference chairman's message

Dear Friends and Colleagues,

On behalf of the Organising Committee it is with great pleasure that I invite you all to our fourteenth congress and the fourth meeting since the International Society of Ocular Oncology was founded only eight years ago in Amsterdam in 2001. Although our Society was 24 years in the making, like a fine wine it has undoubtedly benefited from maturing so slowly.

In the year of this university's 800th anniversary, the International Congress of Ocular Oncology 2009 returns to the Cambridge home of the first meeting in 1977; and also to St John's College where that conference was born as part of the Cambridge Symposium.

I believe that the unique and historic academic environment of a Cambridge college offers us the ideal conditions for formal and informal scientific discourse. It is for this reason that I am pleased that so many of you have chosen to stay in college.

I confess to another motive for choosing Cambridge for the present congress. Hyla Stallard, who introduced practical radiation brachytherapy to the world, was educated in this university at Gonville and Caius College where I too began my career in medicine. Stallard was the second of my illustrious predecessors at Saint Bartholomew's and Moorfields Hospitals in London and the effective founder of ocular oncology as a specialist subject in Britain.

Indeed, the Oncology Service was one of the first sub-specialist clinics to be founded in Moorfields. It is with these facts in our thoughts, and 83 years after our clinic began its life, that we wanted to honour Stallard here with his own medal lecture as one of the founding fathers of the subject we all love.

I do hope that more of you will

consider active membership of ISOO. In a growing Society like ours, that as yet has no formal, salaried administration, the organisation of a conference is undoubtedly an increasingly onerous task and your subscriptions are needed to support the administrative burden that inevitably falls on the voluntary officers.

It is your Society and it can only be as good as you are prepared to make it. Meanwhile, I should like to recognise the immense support that I have received from colleagues in Cambridge Conferences, the Medical Illustration Department of St Bartholomew's Hospital, our local ICOO 2009 Organising Committee, and, of course, our sponsors without whom my task would have been unachievable.

As it casts its net wider and wider, our Society threatens to become a victim of its own undoubted success. Each year since our early meetings, attended by only a few dozen people, our conferences have grown so that we have found it more and more difficult to give sufficient time to the exceptionally high quality material that has been submitted. I know that most of us miss the ample discussion time that we enjoyed in those early days. Nevertheless, and with this in mind, we felt that living under one roof and enjoying college life we would be able to continue to talk informally amongst ourselves long after the formal sessions are over. I do wish you all a very enlightening and enjoyable meeting.

John Hungerford
Chairman of ICOO 2009

Lecturers

Keynote lecturer (Wednesday 9th September, 10.40)

Geoffrey Rose

Mr Geoffrey Rose graduated as Bachelor of Science in Pharmacology, with first-class honours, in 1976. He qualified in Medicine at King's College Hospital Medical School, University of London, in 1979 and subsequently gained experience in internal medicine with award of Membership of the Royal College of Physicians in 1982. Postgraduate ophthalmic training was undertaken at King's College Hospital, St Thomas Hospital and Moorfields Eye Hospital, with award of Fellowship of the Royal College of Surgeons in 1985 and of the Royal College of Ophthalmologists at its foundation in 1988.

In 1990 the University of London granted him an MS doctorate for his research on corneal endothelial changes after cataract surgery and, in 2004, awarded him a Doctor of Science in Ophthalmology and Ophthalmic Surgery.

Mr Rose was appointed as Consultant surgeon to Moorfields Eye Hospital in 1990 and specialises in orbital and lacrimal diseases and surgery. The unique clinical case-mix at Moorfields, in terms of numbers and type of pathology, has provided opportunity for widespread research interests and publication of over 150 papers and articles on adnexal disease. He lectures widely at national and international level and has presented various named and guest lectures. In 2004 he was awarded the Lester Jones Anatomy Award of the American Society of Ophthalmic Plastic and Reconstructive Surgery (of which he is an honorary member).

For 8 years Mr Rose served as the British Council member of the European Society of Ophthalmic Plastic and Reconstructive Surgery, and is President of the British Oculo-Plastic Surgical Society.

Keynote lecturer (Wednesday 9th September, 12.10)

David Verity

Trained in ophthalmology on the South Thames rotation, Mr Verity undertook Fellowships in ophthalmic adnexal disease in Maidstone and Moorfields Eye Hospitals. In 2004 he joined the Moorfields adnexal group, and now specialises in complex lacrimal and orbital disorders, in addition to maintaining a broad interest in the management of lid diseases.

He is an active teacher at both national and international levels, and enjoys the challenge of providing concise didactic lectures on a wide range of subjects. With a research background in ocular inflammation, he has over 60 publications and book chapters in the fields of immunogenetics and eyelid, lacrimal and orbital disease.

He is a Full Member of the British Oculoplastic Surgery Society (BOPSS) and the European Society of Ophthalmic Plastic and Reconstructive Surgery (ESOPRS). In 2009, he was privileged to have been elected to the Orbital Society.

Keynote lecturer

(Wednesday 9th September, 15.40)

Edoardo Midena

Edoardo Midena was born in Venice, Italy. He graduated in Medicine and Surgery, and received his PhD from the University of Padova.
He is Board Certified in Ophthalmology, and now Full Professor of Ophthalmology and Visual Sciences at the University of Padova, School of Medicine, and Chairman of the Department of Ophthalmology, Padova University Hospital.

He is member of the scientific board of the Fondazione GB Bietti per l'Oftalmologia (Roma, Italy). He is elected member of the Club Jules Gonin, the Retina Society and the Macula Society, active member of the American Academy of Ophthalmology, EURETINA, EVER and ISOO, member of the Diversity Committee of the Association for Research in Vision and Ophthalmology, General Secretary of the Italian Retina Society, and a national delegate in the European Board of Ophthalmology. After having served for two terms as Secretary, he is now the Chairman of the European Ophthalmic Oncology Group.

He has been trained in ophthalmic oncology at major international centres. In the sub-speciality field of ophthalmology, he has personally contributed to develop and diffuse: cytodiagnosis of ocular and adnexal tumors, topical chemotherapy of ocular surface tumors, and in vivo detection of chromosomal abnormalities in uveal melanoma. He has also contributed to understanding of the pathophysiology of radiation side effects to the different ocular tissues. He has been invited to give lectures about these topics at major international clinical and research centres, and during international meetings and symposia. In 1993 he founded the Ophthalmic Oncology Service of Padova University Hospital, and he has been recently appointed to head the Ocular Oncology and Toxicology Research Branch of the Fondazione GB Bietti.

He has written three books and many peer-reviewed papers, and edited four volumes. He is a recipient of the SOE European Leadership Development Program in Ophthalmology and AAO Achievement Award.

Keynote lecturer
(Thursday 10th September, 10.40)

J William Harbour

William Harbour, MD, is the Paul Cibis Distinguished Professor at Washington University in St. Louis, where he is director of the Ocular Oncology Service and holds appointments in Ophthalmology and Visual Sciences, Cell Biology and Physiology, and Medicine-Molecular Oncology. He received his baccalaureate degree Summa Cum Laude from Texas A and M University, and his MD from Johns Hopkins. He completed his residency at Wills Eye Hospital, a retina fellowship at Bascom Palmer Eye Institute, and an ocular oncology fellowship at the University of California, San Francisco.

He has an active scientific laboratory that focuses on molecular research into intraocular tumors. In particular, his work has provided new insights into uveal melanoma that has led to a state-of-the-art molecular prognostic test that has been validated in an international, multi-center study and will soon be available as a standard clinical test. He has trained dozens of clinical and research fellows and has received millions of dollars in research funding, including a K08 Physician-Scientist Award from the National Eye Institute, R01 awards from the National Eye Institute and National Cancer Institute, an RPB Research Career Development Award, a Macula Society Research Award, translational research awards from the Barnes-Jewish Hospital Foundation, Kling Family Foundation, Tumori Foundation, Knights Templar Foundation and other organizations.

He serves as associate editor for Melanoma Research, is an editorial board member for the Archives of Ophthalmology, and a regular reveiwer for dozens of journals in the fields of ophthalmology, oncology, cancer research, genetics and molecular biology. He has published over 100 clinical and scientific articles, abstracts and book chapters, has given over 100 invited and named lectures, and has organized dozens of courses and symposia in the field of ocular oncology.

He is a past recipient of the Howard Hughes Medical Institute Research Fellowship, Heed Award, Heed-Knapp Award, Cogan Award from ARVO, and the Rosenthal Award from the Macula Society. He is listed in the Best Doctors in America, America's Top Doctors, and other surveys of distinguished physicians.

Keynote lecturer

(Friday 11th September, 10.40)

Laurence Desjardins

Born 1953. Married with two children. Baccalaureat in 1970. Medical school and ophthalmology in Paris University until 1981, training at Edward Harkness Eye Institute New York from September 1977 to September 1978, fellowship with Pr Haye at Necker Children's Hospital and at the Curie Institute from 1981 to 1984, Head of Department of Ophthalmology at Le Mans Hospital from 1984 to 1987, Assistant in Ophthalmology at the Curie Institute from 1987 to 1991 and Head of Department of Ophthalmology since 1991 in the Curie Institute.

Member of OOG, ISOO, French Society of Ophthalmology and French Society of Paediatric Oncology; President of the OOG from 2003 to 2008; Treasurer of the French Society of Ophthalmology since 2008; President of Honor of Retinostop; Légion d'honneur 2009.

Laurence has been working full time since 1991 in ophthalmic oncology at the Curie Institute.

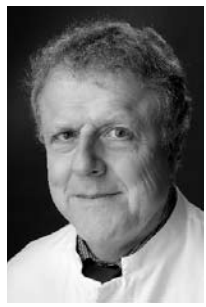
The department treats 300 new cases of uveal melanoma each year and 60 new cases of retinoblastoma plus conjunctival lid and orbital tumors.

She has been the coordinator of several research protocols on uveal melanoma and retinoblastoma and is still responsible for the uveal melanoma working group in the Curie Institute. She has been the coordinator of the French working group on uveal melanoma for the National Cancer Centre (INCA) since 2008 and organiser of the EBO course for ophthalmic oncology. She is the author or co-author of 122 publications on ophthalmic tumors and contributor to three books on ophthalmic tumors.

She has organised two meetings at the Curie Institute, a retinoblastoma symposium in 2003 and a uveal melanoma workshop in 2007. She has been invited to speak in many meetings (WOC, SOE and various local society meetings).

Frezzotti lecturer

(Thursday 10th September, 16.15)



Norbert Bornfeld

Date of birth: 4 June 1952

1970-1976
Medical studies at universities in Bochum and Essen

1976-1977
Intern in Internal Medicine, Surgery and Ophthalmology (University of Essen)

2.9.1977
State examination

1977-1981
Resident in the Department of Ophthalmology at the University of Essen (Prof. Meyer-Schwickerath, Prof. Wessing)

11.3.1980
Medical thesis

1982 - 10/1992
Post doc and fellow in the Department of Ophthalmology at the University of Essen (Prof. Meyer-Schwickerath, Prof. Wessing)

1988
Habilitation

1.10.1992
Full Professor of Ophthalmology at the Free University Berlin, Department of Ophthalmology

1.4.1998
Full Professor of Ophthalmology and Head of the Department for Posterior Segment Diseases, University of Essen

24.6.2009
Elected Member of the European Academy of Ophthalmology

Stallard lecturer

(Friday 11th September, 15.40)

David Abramson

David H. Abramson, MD is the first Chief of the Ophthalmic Oncology Service at Memorial Sloan-Kettering Cancer Center where he is the only physician to have simultaneous appointments in Surgery, Pediatrics and Radiation Oncology. In addition he is Professor of Ophthalmology at the Weill Cornell Medical Center.

After graduation from Harvard College, the Albert Einstein College of Medicine and a medical internship, he did his ophthalmology residency at the Edward S. Harkness Eye Institute where he met Algernon B. Reese, MD and Robert M. Ellsworth, MD and D. Jackson Coleman, MD. While a resident Reese offered him the opportunity to assist him in the writing of his third (and final) version of his text "Tumors of the Eye and Adnexae."

He spent time at the Armed Forces Institute of Pathology with Lorenz E. Zimmerman, MD where he began a lifelong study of second cancers in retinoblastoma. Following the residency he stayed at Columbia where he received a Heed Fellowship to study ophthalmic oncology under Ellsworth. He then joined Ellsworth and in 1994 was named the Director of Ophthalmic Oncology at the Weill Cornell Medical Center in New York.

Dr. Abramson is the author of nearly 500 publications and has collaborated extensively with scientists and clinicians worldwide. He has been on the faculty of Harvard, Columbia, Cornell and a visiting lecturer throughout the United States.

He has worked with physicians in third world countries, especially Latin America where he helped establish ophthalmic oncology services and research.

He has received a number of awards, including being the First

Marshal of his Harvard Class where he was inducted into the Harvard University Athletic Hall of Fame, the Weisenfeld Award from ARVO, the Honor, Senior Honor and Lifetime Achievement from the American Academy of Ophthalmology, the Franceschetti Medal, the Hobart Award from the NY State Ophthalmological Society, the Dorothy Rodbell Cohen Award from Cornell University, the Manhattan League of the Helen Keller Services for the Blind Award, the Charles May Lecture (NY Academy of Medicine), the Robert M. Ellsworth Lecture, Dunnington lecture, Philip E.P. Ellis Lecture, the Alper Memorial lecture and Schoenberg lecture.

He has repeatedly been cited as one of the “best” physicians in New York, the Metro Area, and the U.S. and cited as such in both Ophthalmology and Oncology by Castle Connelly.

Programme

Tuesday
8th September 2009

Research day

Organised by William Harbour

Tuesday 8th September 2009

ICOO research day

Focus on angiogenesis, immunology and epigenetics of ocular tumors

Introduction

8.30 **William Harbour**

Angiogenesis

Moderators: Kyle McKenna and Jose Pulido

8.30–8.45 **Angiogenesis and tumour progression**
Ana Schor

8.45–8.50 **Questions**

8.50–9.05 **Bevacizumab for the control of uveal melanoma in vitro and in vivo**
Hans Grossniklaus

9.05–9.10 **Questions**

9.10–9.25 **Ocular tumor vascular development: tumor angiogenesis and regionalization of vascular progression**
Timothy Murray

9.25–9.30 **Questions**

9.30–9.45 **Uveal melanoma: is the angiogeneic switch turned on?**
Martine Jager

9.45–9.50 **Questions**

9.50–10.05 **Panel discussion** (facilitated by moderators)
Drs Schor, Grossniklaus, Murray, Jager

10.05–10.20 **Coffee**

Immunology

Moderators: Tim Murray and Hans Grossniklaus

10.20–10.35 **The role of age and macrophages in tumor growth in an eye tumor model**
Long Ly

10.35–10.40 **Questions**

10.40–10.55 **Immune evasion by uveal melanoma**
Kyle McKenna

10.55–11.00 **Questions**

11.00–11.15 **A novel immunotherapy that activates retinoblastoma-specific CD4+ T cells**
Bruce Ksander

11.15–11.20 **Questions**

11.20–11.35 **The role of regulatory T cells in uveal melanoma**
Jose Pulido

11.35–11.40 **Questions**

11.40–11.55 **NF-kB pathway in uveal melanoma**
Itay Chowers

11.55–12.00 **Questions**

12.00–12.15 **Panel discussion** (facilitated by moderators)
Drs Ly, McKenna, Ksander, Pulido, Chowers

12.15–1.30 **Lunch**

Epigenetics

Moderators: Martine Jager and Sarah Coupland

1.30–1.45 **Epigenetics in uveal melanoma**
Pieter van der Velden

1.45–1.50 **Questions**

1.50–2.05 **Epigenetic profiling reveals distinct patterns of DNA methylation in class 2 uveal melanomas**
J William Harbour

2.05–2.10 **Questions**

2.10–2.25 **Epigenetics and chromosome 3**
Frederic Mouriaux

2.25–2.30 **Questions**

2.30–2.45 **Extensive search for epigenetic alterations in uveal melanoma**
Michael Zeschnigk

2.45–2.50 **Questions**

2.50–3.05 **Panel discussion** (facilitated by moderators)
Drs Van der Velden, Harbour, Mouriaux, Zeschnigk

3.05–3.20 **Tea**

Epigenetics (continued)

Moderators: Brenda Gallie and Bruce Ksander

3.20–3.35 **Detection of hypermethylation of TSGs in ocular adnexal lymphoma using MLPA**
Sarah Coupland

3.35–3.40 **Questions**

3.40–3.55 **Epigenetics of retinoblastoma**
Dietmar Lohmann

3.55–4.00 **Questions**

4.00–4.15 **Functional implications of beta-arrestins and MDM2 on invasive behavior of uveal melanoma cells**
L Girnita

4.15–4.20 **Questions**

4.20–5.00 **Panel discussion** (facilitated by moderators)
Drs Coupland, Lohmann and Girnita

Wednesday
9th September 2009

Orbital, eyelid and epibulbar tumours

Session 1

Orbital tumours

Orbital tumours - diagnosis

Orbital tumours - pathology

Orbital tumours - treatment

Wednesday 9th September 2009

8.15–8.30 **Introduction**

Orbital, eyelid and epibulbar tumours

Session 1
Chairs: G Rose, C Stannard, R Eagle

Orbital tumours

Orbital tumours – diagnosis

8.30–8.35 **Trephine biopsy of orbital tumors**
Yarovoy AA, Bulgakova ES, Shatskih AV, Uzunyan DG, Kleyankina SS

8.35–8.40 **Orbital MALT lymphoma versus orbital mantle cell lymphoma**
Grishina EE, Guzenko ES

Orbital tumours – pathology

8.40–8.45 **Orbital schwannoma: a clinicopathologic study**
Shrey D, Pushker N, Bajaj MS, Mehta M, Sen S, Kashyap S, Ghose S

8.45–8.50 **Pathogenesis of orbital tumours with clinical implications in Maadi AF Hospital Cairo**
Assem M

Orbital tumours – treatment

8.50–8.55 **Iodine-125 orbital brachytherapy with a prosthetic implant in situ**
Stannard C, Maree G, Munro R, Lecuona K, Sauerwein W

8.55–9.00 **Cyberknife radiotherapy for the treatment of ocular and periocular lymphoma**
Lally SE, Bianciotto C, Shields CL, Shields JA

9.00–9.05 **Orbital exenteration: the Moorfields 25-year experience**
Saleh GM, Morris O, Beaconsfield M, Verity DH, Uddin J, Rose GE, Collin JRO

9.05–9.10 **Embolisation of distensible venous malformations of the orbit (varices) after direct surgical exposure: a preliminary study**
Xiao L, Zhong X, Wang Y

9.10–9.15 **Angiolymphoid hyperplasia with eosinophilia of the orbit: clinical presentation and treatment results of a rare disease in four patients**
Briscoe D, Cruz AA, Chahud F, Procianoy F, Kidron D

9.15–9.30 **Discussion**

Wednesday
9th September 2009

Orbital, eyelid and epibulbar tumours

Session 2

Orbital tumours

Orbital tumour case reports

Keynote lecture

Wednesday 9th September 2009

Orbital, eyelid and epibulbar tumours

Session 2

Chairs: J Shields, R Whitelocke, D Gombos

Orbital tumours

Orbital tumour case reports

9.30–10.40

Orbital schwannoma with fluid-fluid levels on MRI

Gündüz K[1], Erden E[2]
[1]Department of Ophthalmology and [2]Pathology, Ankara University Faculty of Medicine, Ankara, Turkey

An unusual orbital solitary fibrous tumor

Alemany-Rubio E[1], Parrozzani R[1], Urban F[1], Pilotto E[1], Midena E[1,2]
[1]Department of Ophthalmology, University of Padua, Padua, Italy
[2]GB Bietti Eye Foundation, IRCCS, Rome, Italy

Orbital carcinoid: first or second ocular metastasis?

Bernardino CR, Liggett PE
Yale Eye Center/Yale University School of Medicine, Yale, USA

Orbital lymphangioma manifested with intraocular hemorrhage

Kao LY
Chang Gung Memorial Hospital, Chang Gung University, Taipei, Taiwan

Orbital vascular collision tumour

Briscoe D, Mukari A, Zahavi T
Meir Medical Center Kfar Saba Israel, Haemek Medical Center, Afula, Israel

Malignant metastatic myoepithelioma of the lacrimal gland

Calle-Vasquez A
Calle Orbital and Oncology Center, Bogota, Columbia

Angiomyxoma of the orbit

Calle-Vasquez A
Calle Orbital and Oncology Center, Bogota, Columbia

Melanoma of the orbit

Furdova A, Chynoransky M
Department of Ophthalmology, Comenius University Medical School, Bratislava, Slovakia

Orbital tumor in children: Wegener's granulomatosis

Chipczyńska B, Grałek M, Hautz W
The Children's Memorial Health Institute, Warsaw, Poland

Rosai-Dorfman disease (sinus histiocytosis with massive lymphadenopathy) with isolated bilateral lacrimal enlargement presenting hyper serum IgG4 concentration

Furuta M[1], Sugano Y[1], Oguchi Y[1], Kiko Y[2] Lida T[1]
[1]*Department of Ophthalmology, Fukushima Medical University School of Medicine, Japan*
[2]*Department of Pathology, Fukushima Medical University School of Medicine, Japan*

Prenatal detection of orbital mass

Singh AD
Department of Ophthalmic Oncology, Cole Eye Institute, Cleveland Clinic, Cleveland, OH, USA

Keynote lecture

10.40–11.00 **Current concepts in management of lacrimal gland tumours**

Geoffrey Rose
Moorfields Eye Hospital, London, UK

11.00–11.15 Coffee and posters

Wednesday
9th September 2009

Orbital, eyelid and epibulbar tumours

Session 3

Eyelid tumours

Eyelid tumours - basal cell carcinomas

Eyelid tumours - lymphomas

Eyelid tumours - treatment

Eyelid tumours case reports

Keynote lecture

Wednesday 9th September 2009

Orbital, eyelid and epibulbar tumours

Session 3

Chairs: D Verity, B Esmaeli, S Seregard

Eyelid tumours

Eyelid tumours - basal cell carcinomas

11.15–11.20 **Infundibulocystic basal cell carcinoma of the eyelid in basal cell nevus syndrome**

Brownstein S, Belliveau MJ, Coupal DJ, Jordan DR, Prokopetz R

11.20–11.25 **Basal cell carcinoma of eyelid skin can be induced by enhanced DNA polymerase iota activity**

Grishina EE, Gening LV, Kazakov AA, Petrochenkov AN, Tarantul VZ

Eyelid tumours - lymphomas

11.25–11.30 **Spectrum of CD30+ lymphoid proliferations in the eyelid**

Grossniklaus HE, Sanka RK, Eagle Jr RC, Wojno TH, Neufeld KR

11.30–11.35 **Newly classified EBV positive diffuse large B-cell lymphoma of the elderly in the eyelid and orbit**

Tsuji H, Tamura M, Takeuchi K, Kojima T

Eyelid tumours - treatment

11.35–11.40 **Non-surgical treatment for eyelid tumors**

Calle-Vasquez A, Vianna CH, Daza MT

11.40–11.45 **High-dose-rate interstitial brachytherapy as an alternative to exenteration in recurrent squamous cell carcinoma of the eyelid**

Mahesh L, Mahesh Shanmugam P, Sharma S

Eyelid tumours case report

11.45–11.48 **A case of apocrine adenocarcinoma of the eyelid**

Takahira M, Zen Y, Sugiyama K
Kanazawa University Hospital, Kanazawa, Japan

11.48–12.10 **Discussion**

Keynote lecture

12.10–12.30 **Indolent lid changes, life-threatening lesions**
David Verity
Moorfields Eye Hospital, London, UK

13.00–14.00 **Business meeting and lunch**

Wednesday
9th September 2009

Orbital, eyelid and epibulbar tumours

Session 4

Epibulbar tumours

Epibulbar tumours - differential diagnosis

Conjunctival melanoma - aetiology

Conjunctival melanoma - diagnosis

Conjunctival melanoma - sentinel node biopsy

Conjunctival melanoma - treatment

Squamous carcinoma - diagnosis

Squamous carcinoma - treatment

Haemangioma

Epibulbar tumours case reports

Keynote lecture

Wednesday 9th September 2009

Orbital, eyelid and epibulbar tumours

Session 4

Chairs: J Muecke, J Pe'er, V Cohen

Epibulbar tumours

Epibulbar tumours - differential diagnosis

14.00–14.05 **The differential diagnosis of localised amelanotic limbal lesions: a review of 171 consecutive excisions**

Rudkin AK, Dodd T, Muecke JS

14.05–14.10 **Conjunctival tumors in a Hispanic population: clinical series of 100 patients from Chile**

Mánquez ME, Vigorena P

Conjunctival melanoma - aetiology

14.10–14.15 **Conjunctival melanoma: the major role of primary acquired melanosis in local recurrences and metastatic disease**

Levy-Gabriel C, Plancher C, Sastre X, Lumbroso-Le Rouic L, Asselain B, Dendale R, Desjardins L

Conjunctival melanoma - diagnosis

14.15–14.20 **Ultrasound biomicroscopic observation of conjunctival melanoma**

Wei WB

Conjunctival melanoma - sentinel node biopsy

14.20–14.25 **Sentinel lymph node biopsy in the management of conjunctival melanoma**

Cohen V, Ahmed N, Moir G, Jan H, Hungerford J

14.25–14.30 **Sentinel lymph node biopsy for conjunctival and eyelid melanoma: experience in 30 patients**

Esmaeli B, Savar A, Ross MI, Prieto VG, Ivan D

Conjunctival melanoma - treatment

14.30–14.35 **Strontium-90 beta radiotherapy for the adjuvant treatment of conjunctival melanoma**

Liu S, Cohen VML, Hungerford JL

Squamous carcinoma - diagnosis

14.35–14.40 **Pre-operative exfoliative cytology versus histopathology of squamous cell carcinoma of the conjunctiva and cornea**

Semenova EA, Milman T, Kurli M, Schneider S, Natesh S, Iacob CE, McCormick SA, Finger PT

14.40–14.45 **The use of 1% toluidine blue eye drops in the diagnosis of ocular surface squamous neoplasia**

Ballalai PL, Romero IL, Barros JN, Gonçalves LS, Martins MC

Squamous carcinoma - treatment

14.45–14.50 **Surgery and additional proton therapy for treatment of invasive and recurrent squamous cell carcinomas: technique and preliminary results**

Maschi C, Caujolle JP, Chauvel P, Herault J, Gastaud P

14.50–14.55 **The treatment of squamous cell carcinoma of the conjunctiva with excision and beta irradiation**

Lecuona KA, Stannard C, Hart G, Myer L, Wetter J

14.55–15.00 **The use of 5-Fluorouracil in the treatment of ocular surface squamous neoplasia**

Muecke JS, Rudkin AK

15.00–15.05 **Long-term corneal toxicity of topical chemotherapy with 1% 5-Fluoruracil: a confocal microscopy analysis**

Parrozzani R, Urban F, Miotto S, Lazzarini D, Alemany-Rubio E, Midena E

15.05–15.10 **Conjunctival intra-epithelial neoplasia occurring in young patients with asthma**

Rundle P, Mudhar HS, Rennie I

Haemangioma

15.10–15.15 **Photodynamic therapy in combined treatment of conjunctival hemangioma**

Aubakirova A, Sarsembekova K, Abdullina V, Zhakybekov R

Epibulbar tumours case reports

15.15–15.30

Conjunctival pigmentation and topical prostaglandin analogues

Giblin M
Sydney Eye Hospital, Sydney, Australia

Metastatic conjunctival squamous cell carcinoma

Ikatan H, Al-Motlak M
King Khalid Eye Specialist Hospital, Saudia Arabia

A pink conjunctival tumour in a two-year-old girl

Toft PB
Eye Clinic, Rigshospitalet, Denmark

Violaceous expansile conjunctival lesion in an African American HIV+ male

Mruthyunjaya P[1], Cummings T[2], Kim T[3], Proia A[4]
Departments of [1]Ocular Oncology and Vitreoretinal Surgery, [2]Pathology, [3]Cornea and Refractive Surgery and [4]Pathology, Duke University Medical Center, Durham, NC, USA

15.30–15.40 **Discussion**

Keynote lecture

15.40–16.00 **Squamous neoplasia: more than meets the eye**

Edoardo Midena
Department of Ophthalmology, University of Padua, Padua, Italy

16.00–16.15 **Tea and posters**

Wednesday
9th September 2009

Uveal tumours

Session 5

Uveal tumour case reports (1)

Wednesday 9th September 2009

Uveal tumours

Session 5

Chairs: J Shields, R Whitelocke, D Gombos, A Arora

Uveal tumour case reports (1)

16.15–18.00

Pigmented cystic Axenfeld's nerve loop associated with melanocytic cilio-choroidal lesion

Correa ZM, Simoes CC, Augsburger JJ
University of Cincinnati College of Medicine, Department of Ophthalmology, Cincinnati OH, USA

Peripheral choroidal mass with subretinal exudation: what is your diagnosis?

Othman IS
Cairo University and The National Eye Center, Egypt

Cellular uveal schwannoma in a patient with PTEN hamartomatous syndrome

Moulin A, Uffer S, Zografos L
University Eye Clinic, Lausanne, Switzerland

Atypical presentation of ciliary body medulloepithelioma

Ali MJ, Honavar SG, Vemuganti GK
LV Prasad Eye Institute, Banjara Hills, Hyderabad, Andhra Pradesh, India

A rare case of malignant medulloepithelioma

Sarsembekova K, Aubakirova A
Kazakh Research Institute of Eye Diseases, Almaty, Kazakhstan

Pediatric glaucoma treated with seton placement in eyes harboring medulloepithelioma

Gombos DS, Chevez-Barrios P, Boniuk M
MD Anderson Cancer Center, The Methodist Hospital and The Baylor College of Medicine, Houston Texas, USA

Adult malignant hypopyon following multiple surgeries: a diagnostic dilemma

Othman IS
Cairo University and The National Eye Center, Egypt

Fatal choroidal melanoma in twins

Tuomaala R, Kivelä T
Ocular Oncology Service, Department of Ophthalmology, Helsinki University, Finland

Iridociliary mass in an infant for differential diagnosis

Othman IS
Cairo University and The National Eye Center, Egypt

Choroidal tumour in a 7-year-old girl

Damato B, Coupland SE
School of Cancer Studies, Liverpool, UK

Melanocytic intraocular tumor in a black teenager

Li HK
Ocular Oncology Service, Wills Eye Institute, Thomas Jefferson University, Philadelphia, PA, USA

Amelanotic choroidal tumour in a young patient

Angi M[1], Cassoux N[1], Lumbroso-Le Rouic L[2],Levyc C[2],Desjardins L[2]
[1]Department of Ophthalmology, Pitie-Salpetriere University Hospital, Paris, France
[2]Department of Ocular Oncology, Institut Curie, Paris, France

Rapid growth of uveal melanoma during pregnancy

Lee CS[1], Lee S-C[1], Yang WI[2], Shin KJ[3]
[1]Department of Ophthalmology, [2]Department of Pathology, [3]Department of Forensic Medicine, Yonsei University College of Medicine, Seoul, Korea

Growing iris naevi – is that a melanoma?

Hadden PW
University of Auckland, New Zealand

Multicentric tapioca melanoma of the iris

Eagle RC Jr, Shields JA, Shields CL
Department of Pathology and Oncology Service, Wills Eye Institute, Philadelphia, USA

A case of (juvenile) xanthogranuloma of the iris simulating melanoma in an adult

Faber RT, Eide NA Haaland TK
Department of Ophthalmology, Ullevål Hospital, University of Oslo, Norway

Unusual ciliary body tumor in a middle-aged man: diagnosis and natural course

Mashayekhi A
Ocular Oncology Service, Wills Eye Institute, Thomas Jefferson University, Philadelphia, PA, USA

Thursday
10th September 2009

Uveal tumours

Session 1

Melanocytic tumours

Uveal naevi

Uveal melanoma - imaging

Uveal melanoma - biopsy

Uveal melanoma - observation

Thursday 10th September 2009

Uveal tumours

Session 1
Chairs: A Singh, J Shields, J-D Grange

Melanocytic tumours

Uveal naevi

8.00–8.05 **Slow enlargement of choroidal nevi: long-term follow-up of 278 patients**
Mashayekhi A, Shields CL, Siu S, Shields JA

8.05–8.10 **Giant choroidal nevus: clinical features and natural course in 322 cases**
Li HK, Shields CL, Mashayekhi A, Randolph JD, Bailey T, Burnbaum J, Shields JA

8.10–8.13 **Very large choroidal nevi**
Singh AD

Uveal melanoma - imaging

8.13–8.16 **Growth prediction in small choroidal melanocytic lesions: a pilot study on N-isopropyl-p-[^{123}I]-iodoamphetamine**
Kubota T, Kato K, Terasaki H

8.16–8.19 **Fundus autofluorescence imaging of choroidal melanocytic tumors**
Pilotto E, Parrozzani R, Urban F, Midena E

8.19–8.22 **Panoramic angiography and ICG in uveal melanomas**
Zografos L, Schalenbourg A, Chamot L

8.22–8.25 **Correlation of fundus autofluorescence with fluorescein and indocyanine green angiography in choroidal melanocytic lesions**
Gündüz K, Pulido JS, Pulido JE, Link T

Uveal melanoma - biopsy

8.25–8.30 **Intraocular biopsies – results and efficacy of uveal biopsies performed by the Essen biopsy forceps in comparison to other biopsy techniques**

Akguel H, Jurklies B, Otterbach F, Goek M, Freistuehler M, Gkika T, Bornfeld N

8.30–8.35 **Fine needle aspiration biopsy versus punch biopsy for the cytogenetic analysis of uveal tract melanoma**

Cohen V, Grantham M, Lillington D, Hungerford J

Uveal melanoma – observation

8.35–8.40 **Observation as a therapeutic option in choroidal melanoma**

García-Álvarez C, Saornil MA, Almaraz A, López-Lara F, Ceballos A, Frutos J, Muiños Y

8.40–8.55 **Discussion**

Thursday
10th September 2009

Uveal tumours

Session 2

Melanocytic tumours

Uveal melanoma treatment
- transpupillary thermotherapy

Uveal melanoma treatment
- photodynamic therapy

Uveal melanoma treatment
- radiation brachytherapy

Uveal melanoma treatment
- charged particle therapy

Keynote lecture

Thursday 10th September 2009

Uveal tumours

Session 2

Chairs: L Desjardins, M Materin, E Gragoudas

Melanocytic tumours

Uveal melanoma treatment - transpupillary thermotherapy

8.55–8.58 **Laser hyperthermia as a method of choroidal melanoma devitalization before its endoresection**

Likhvantseva VG, Sultanova EO, Khatsalap SN

8.58–9.01 **Transpupillary thermotherapy for residual choroidal melanoma and recurrent tumors: preliminary study**

Semenova EA, Saakyan SV, Valsky VV

Uveal melanoma treatment - photodynamic therapy

9.01–9.04 **Treatment of choroidal amelanotic melanoma with PDT**

Campbell WG, Pejnovic TM

Uveal melanoma treatment - radiation brachytherapy

9.04–9.09 **Brachytherapy with ruthenium-106 (Ru-106) plaques for uveal melanoma**

Naseripour M, Nazari H, Ghasemi Falavarjani K, Jaberi R, Oladi M

9.09–9.14 **Long-term results after ^{106}Ru-brachytherapy for uveal melanoma**

Bechrakis NE, Lakotka N, Alekian L, Willerding G, Krause L, Wachtlin J, Foerster MH

9.14–9.17 **Local tumour control after ruthenium^{106} brachytherapy for choroidal melanoma**

Papageorgiou KI, Kinsella M, Cohen V, Bunce C, Hungerford JL

9.17–9.20 **Visual acuity after ruthenium^{106} brachytherapy for choroidal melanoma: a 5 year retrospective review**

Kinsella M, Cohen V, Papageorgiou KI ,Bunce C,Hungerford JL

9.20–9.23 **Ophthalmic brachytherapy using indigenous BARC Ocu-Prosta Iodine-125 seeds for treatment of choroidal melanomas in India**

Shah PK, Narendran V, Selvaraj U, Guhan P, Saxena SK, Dash A, Venkatesh M, Astrahan M

9.23–9.26 **High dose rate ^{169}Ytterbium brachytherapy with a collimated applicator for treatment of intraocular melanoma**

Munro JJ, Zaider M, Abramson DH, Cohen G, Medich DC

9.26–9.29 **Growth in tumour thickness of medium-sized uveal melanoma before ^{125}Iodine brachytherapy as a predictor for post-treatment tumour behaviour**

Simpson ER, Krema H, Pavlin CJ, Xu W, Law C, Riveros L

9.29–9.32 **Tumour regression after brachytherapy for uveal melanoma: relationship between reduction in tumor height and cross-sectional area**

Rashid MM, Kivelä T

9.32–9.35 **Blood circulation in retina in early terms after brachytherapy of uveal melanomas**

Amiryan AG, Saakyan SV

9.35–9.38 **Combined pars plana vitrectomy cataract extraction and endolaser ablation for treated uveal melanoma**

Cebulla CM, Sisk RR, Markoe AM, Dubovy SR, Murray TG

Uveal melanoma treatment - charged particle therapy

9.38–9.43 **Charged particle therapy of uveal melanoma**

Char D, Mishra K, Phillips TL

9.43–9.48 **Sixteen years of proton beam radiotherapy for uveal melanomas at Nice Teaching Hospital**

Caujolle JP, Pinon F, Mammar H, Chamore E, Herault J, Gastaud P

9.48–9.53 **Complications after proton beam therapy for choroidal and ciliary body melanomas with initial height of 7mm or more: a 15 years experience, 1991–2006**

Grange JD, Nguten M, Jean-Louis B, Kodjikian L

9.53–9.58 **Treatment of post-proton therapy neovascular glaucoma (NVG) with intravitreal anti-VEGF: preliminary results and research project**
Freton A, Caujolle JP, Pinon F, Gastaud P

9.58–10.03 **Visual outcomes after proton beam irradiation for choroidal melanomas involving the macula**
Kim IK, Lane AM, Gragoudas ES

10.03–10.06 **Eye retention and survival rate following proton beam therapy for uveal melanoma in Scotland**
Macdonald ECA, Cauchi P, Kemp K

10.06–10.09 **Long-term survival in patients with uveal melanoma treated with proton therapy**
Gragoudas ES, Lane AM, Kim IK

10.09–10.12 **Treatment of juxtapapillary melanoma: proton beam versus notched ruthenium plaque brachytherapy**
Henderson RH, Foss AJE, Cohen V, Hungerford J

10.12–10.15 **Proton beam irradiation in choroidal melanoma with sizeable extraocular extension**
Willerding GW, Moser L, Bechrakis NE, Foerster MH

10.15–10.18 **Recurrence of the uveal melanoma in the orbit: abilities of proton beam irradiation**
Valsky VV, Saakjan SV, Borodin YI

10.18–10.40 **Discussion**

Keynote lecture

10.40–11.00 **A decade of discovery, innovation and hope in the management of uveal melanoma**
William Harbour
Department of Ophthalmology and Visual Sciences, Washington University School of Medicine, St. Louis, Missouri, USA

11.00–11.15 **Coffee and posters**

Thursday
10th September 2009

Uveal tumours

Session 3

Melanocytic tumours

Uveal melanoma treatment
- stereotactic radiosurgery

Uveal melanoma treatment
- electroporation

Uveal melanoma treatment
- radiation retinopathy

Uveal melanoma treatment
- local resection

Thursday 10th September 2009

Uveal tumours

Session 3

Chairs: N Bornfeld, D Char, B Damato

Melanocytic tumours

Uveal melanoma treatment - stereotactic radiosurgery

11.15–11.18 **Macular morphological changes following stereotactic radiosurgery for uveal melanoma**

Furdova A, Svorenova I, Sramka M, Chorvath M, Strmen P

11.18–11.21 **Comparison between ^{125}Iodine brachytherapy and stereotactic radiotherapy in the management of juxtapapillary choroidal melanoma**

Krema H, Simpson ER, Heydarian M, Beiki-Ardakani A, Xu W, Weisbrod D, Payne D

Uveal melanoma treatment - electroporation

11.21–11.24 **Irreversible electroporation for uveal melanoma: a possible new treatment modality**

Mandel Y, Pe'er J, Frenkel S, Rubinsky B

Uveal melanoma treatment - radiation retinopathy

11.24–11.27 **Proliferative radiation retinopathy following plaque radiotherapy for uveal melanoma**

Bianciotto C, Shields CL, Pirondini C, Mashayekhi A, Furuta M, Shields JA

11.27–11.30 **Treatment of radiation oculopathy due to I-125 brachytherapy of uveal melanoma with intravitreal bevacizumab, transpupillary thermotherapy, and surgery**

Hovland PG, Hovland KR

11.30–11.33 **Sector laser photocoagulation for prevention of macular edema following plaque radiotherapy for uveal melanoma**

Materin MA, Shields CL, Bianciotto C

11.33–11.36 **A pilot study comparing the efficacy of intravitreal bevacizumab versus intravitreal triamcinolone in the treatment of macular oedema following plaque radiotherapy for uveal melanoma**

Horgan N, Shields CL, Mashayekhi A, Shields JA

Uveal melanoma treatment - local resection

11.36–11.39 **Trans-scleral resection of choroidal melanoma**

Damato BE, Groenewald C, Coupland SE

11.39–11.42 **Long-term results after endoresection with pre-treatment by single-dose stereotactic convergence irradiation and adjuvant brachytherapy in large uveal melanomas**

Freistühler M, Biewald E, Akgül H, Horstmann GA, Bornfeld N

11.42–11.45 **Vitreoretinal surgery and endoresection in posterior choroidal melanoma after radiotherap**y

Mayer C, Wackernagel W, Langmann G, Schneider M, Wedrich A

11.45–11.48 **Cataract extraction and implantation of an artificial iris with IOL after block excision of iridociliary tumours**

Saakyan SV, Chentsova EV, Andreeva TA

11.48–12.00 **Discussion**

Thursday
10th September 2009

Uveal tumours

Session 4

Melanocytic tumours

Uveal melanoma metastases - incidence

Uveal melanoma metastases - detection

Uveal melanoma metastases - prevention

Uveal melanoma metastases - growth

Uveal melanoma metastases - treatment

Uveal melanoma metastases - markers

Thursday 10th September 2009

Uveal tumours

Session 4

Chairs: S Seregard, L Zografos, E Midena

Melanocytic tumours

Uveal melanoma metastases - incidence

12.00–12.05 **Metastasis of iris, ciliary body, and choroidal melanoma in 8,033 patients**

Shields CL, Furuta M, Thangappan A, Nagori S, Nutheti R, Mashayekhi A, Shields JA

12.05–12.08 **CNS metastasis from malignant uveal melanoma: a clinical and histopathological characterisation**

Lindegaard J, Holfort SK, Isager P, Prause JU, Heegaard S

Uveal melanoma metastases - detection

12.08–12.11 **Whole body PET/CT: initial screening for metastatic choroidal melanoma**

Raut R, Chin KJ, Finger PT

12.11–12.14 **MRI versus FDG-PET scan in patients with liver metastases from uveal melanoma: a prospective study with intraoperative confirmation**

Malhaire C, Mariani P, Servois V, Petras S, Piperno-Neumann S, Berry MG, Plancher C, Levy-Gabriel C, Lumbroso-Le Rouic L, Desjardins L, Salmon RJ

Uveal melanoma metastases - prevention

12.14–12.17 **Pilot study of adjuvant immuno-chemotherapy for high risk uveal melanoma: a single-center experience with thirty-one patients**

Mazzini C, Pinzani P, Salvianti F, Pazzagli M, Grifoni R, Vannini A, Neri B

Uveal melanoma metastases - growth

12.17–12.20 **The role of nm23 and CD117 in the regulation of uveal melanoma growth**

Anurova OA, Likhvantseva VG, Veretschagina MV

Uveal melanoma metastases - treatment

12.20–12.23 **Response after hyperthermic isolated hepatic perfusion with melphalan for metastatic uveal melanoma**

Sandkull P, Olofsson R, Seregard S, All-Ericsson C, Hjelmqvist L, Cahlin C, Hafström L, Mattsson J, Olausson M, Rizell M, Lindnér P

12.23–12.26 **Applicability to surgically managed patients of the Helsinki University Central Hospital (HUCH) working formulation for staging metastatic uveal melanoma**

Eskelin S, Kivelä T, Piperno-Neumann S, Desjardins L, Schimittel A, Bechrakis N, Midena E, Grange J-D, Ract-Madoux G, Marshall E, Damato B, Leyvraz S, Zografos L

12.26–12.29 **Expression of human cancer-testis antigens, MAGE-A1, -A4, -C1 and NY-ESO-1 in primary human uveal melanoma**

Conway RM, Walsh-Conway N, Browning J, Madigan MC, Klein O, Cebon J

Uveal melanoma metastases - markers

12.29–12.32 **VEGF serum levels as a new marker for metastatic uveal melanoma**

Barak V, Frenkel S, Kalickman I, Pe'er J

12.32–12.35 **Nucleolar size in choroidal and ciliary body melanomas and corresponding hepatic metastases**

Al-Jamal R, Toivonen P, Kivelä T

12.35–12.38 **Comparative proteomic analysis of uveal melanoma serological peptidome**

Li Q, Wei WB

12.38–13.00 **Discussion**

13.00–14.00 **Lunch**

Thursday
10th September 2009

Uveal tumours

Session 5

Melanocytic tumours

Uveal melanoma - extrascleral extension

Uveal melanoma - prognosis

Uveal melanoma - social aspects

Thursday 10th September 2009

Uveal tumours

Session 5

Chairs: T Kivelä, N Bechrakis, M Giblin

Melanocytic tumours

Uveal melanoma - extrascleral extension

14.00–14.05 **Uveal melanoma with extrascleral extension: local treatment and survival**

Desjardins L, Caujolle JP, Bellmann C, Lumbroso-Le Rouic L, Levy C, Dendale R, Plancher C, Sastre X, Asselain B

Uveal melanoma - prognosis

14.05–14.10 **Follow-up study in high-risk uveal melanoma patients**

Servois V, **Piperno-Neumann S**, Mariani P, Couturier J, Plancher C, Levy-Gabriel C, Lumbroso-Le Rouic L, Salmon R, Asselain B, Desjardins L

14.10–14.15 **Predicting the prognosis of ciliochoroidal uveal melanoma by its clinical characteristics: a European Ophthalmic Oncology Group (OOG) study**

Kujala E, Damato B, Coupland S, Desjardins L, Bechrakis N, Grange JD, Kivelä T

14.15–14.18 **Iris color: as a prognostic factor in uveal melanoma**

Muiños Y, Saornil MA, García C, Almaraz A, Muñoz MF, Lopez-Lara F, de Frutos JM

14.18–14.21 **Postlaminar optic nerve invasion – clinicopathological study of 46 enucleated specimens over a period of 11 years**

Nagpal A, Khatri M, Kumar KS, Biswas J, Sharma T, Gopal L, Khetan V

Uveal melanoma - social aspects

14.21–14.24 **Quality of life of uveal melanoma survivors and their family members**

Frenkel S, Rosenne H, Hendler K, Baruch R, Pe'er J

14.24–14.27 **Socioeconomic deprivation and choroidal melanoma in Scotland**

Lockington D, Chadha V, Russell H, Young D, Cauchi P, Kemp E

14.27–14.45 **Discussion**

Thursday
10th September 2009

Uveal tumours

Session 6

Melanocytic tumours

Hot topic uveal melanoma
- the role of cytogenetics and genomics

Thursday 10th September 2009

Uveal tumours

Session 6

Chairs: W Harbour, M Jager, I Rennie

Melanocytic tumours

Hot topic uveal melanoma - the role of cytogenetics and genomics

14.45–14.48 **Characterization of three choroidal melanoma cell lines derived from FNAB of primary tumors with metastatic outcome**

Burgess BL, McCannel TA, Rao NP, Straatsma BR

14.48–14.51 **Relative genetic imbalance (RGI) between chromosome 8 and MYC copy number as an indication of survival in uveal melanoma**

Sisley K, Baigent A, Rennie IG

14.51–14.54 **Sequential probing for subtelomeric arms of chromosome 6 and centromeric chromosome 3 in choroidal melanoma fine needle aspiration biopsies**

McCannel TA, Burgess BL, Rao NP, Straatsma BR

14.54–14.57 **Chromosome 3 status in 500 eyes with uveal melanoma**

Bianciotto C, Shields CL, Ganguly A, Materin M, Shields JA

14.57–15.00 **In-vivo cytogenetic testing of uveal melanoma: seven years of clinical experience**

Midena E, Parrozzani R, Pilotto E, Urban F, Alemany-Rubio E, Bonaldi L

15.00–15.03 **Heterogeneity of gene expression signature in melanocytic uveal tumors sampled at two sites by FNAB**

Augsburger JJ, Correa ZM, Simoes CC, Harbour JW

15.03–15.06 **Gene expression profile (GEP) class versus thickness of melanocytic uveal tumors evaluated by FNAB**

Simoes CC, Correa ZM, Augsburger JJ, Harbour JW

15.06–15.09 **Identification of genetic and epigenetic alterations that may contribute to the pathogenesis of uveal melanoma**

Manokhina IK, Sklyarova NV, Khoroshilova-Maslova IP, Saakyan SV, Zaletayev DV

15.09–15.12 **Transscleral white-light spectroscopy for assessment of melanin content in experimental choroidal lesions**
Krohn J, Xu C, Svenmarker P, Khoptyar D, Andersson-Engels S

15.12–15.15 **Association between gene expression profile classification and cytopathologic cell type of melanocytic uveal tumors evaluated by FNAB**
Correa ZM, Augsburger JJ, Simoes CC, Harbour JW

15.15–15.18 **Clinical relevance of genomic analysis of uveal melanoma**
Coupland SE, Damato B

15.18–15.21 **The p53 pathway in uveal melanoma**
Guo Y, Pajovic S, McGowan HD, Simpson ER, **Gallie BL**

15.21–15.24 **A novel oncogene mutation in uveal melanoma and its clinical relevance**
Harbour JW

15.24–15.27 **KIT oncogene mutations in uveal melanomas**
Belyakov IS, Anurova OA, Mazurenko NN, Likhvantseva VG

15.27–15.30 **Reduced autotaxin expression in uveal melanoma correlates with epithelioid cell type and predicts a poor prognosis**
Rennie IG, Mudhar H, Burn L, Hammond DW, Baigent A, Sisley K

15.30–15.33 **Autotaxin expression in ocular tissue and uveal melanoma**
Schoenfield L, Simmerman K, Singh AD

15.33–15.36 **Next generation sequencing of biomarkers for uveal melanoma metastasis**
Ganguly A, Chao E, Sherrill Mix S, Grant GE, Ganguly T, Shields C

15.36–15.39 **Should pathologists obtain informed consent prior to testing?**
Rasmussen SL, McWhae J, and Bailey TM

15.39–16.00 **Discussion**

16.00–16.15 **Tea and posters**

Thursday
10th September 2009

Uveal tumours

Session 7

Other uveal tumours

Frezzotti lecture

Miscellaneous non-melanocytic uveal tumours

Thursday 10th September 2009

Uveal tumours

Session 7
Chairs: MA Blasi, E Kemp

Other uveal tumours

Frezzotti lecture

16.15–16.35 **Uveal melanoma - from eye salvaging to life saving treatment options**

Professor Norbert Bornfeld
University Hospital of Essen, Department of Ophthalmology, Essen, Germany

Miscellaneous non-melanocytic uveal tumours

16.35–16.38 **Mes(ect)odermal leiomyoma: diagnostic approach and management**

Schalenbourg A, Mormile S, Uffer S, Zografos L

16.38–16.41 **Diagnostic transretinal 25-gauge biopsy of choroidal non-pigmented tumors**

Tiberti AC, Scupola A, Blasi MA, Laguardia M, Balestrazzi E

16.41–16.44 **Metastatic tumors to the iris – clinical presentation and treatment**

Zografos L, Schalenbourg A, Chamot L

16.44–16.47 **Iris and ciliary body masses: gonioscopic and fluorescein angiographic studies, with new observations**

Hassan S, Othman IS

16.47–16.50 **High-frequency ultrasound biomicroscopy role for the differential diagnosis of ciliary body and iris tumors**

Blasi MA, Valente P, Caputo CG, Col Angelo E, Sammarco MG, Balestrazzi E

16.50–16.53 **Photodynamic therapy with Verteporfin for circumscribed choroidal haemangiomas using standard treatment parameters**

Heimann H, Russo A and Damato B

16.53–16.56 **Photodynamic therapy for vasoproliferative tumors and capillary hemangiomas of the retina**
Naseripour M, Ghasemi Falavarjani K, Mirfallah K

16.56–16.59 **Photodynamic therapy salvage following anti-VEGF therapy for choroidal osteoma-associated choroidal neovascularization**
Mruthyunjaya P, Khanifar A

16.59–17.02 **Correlation of fundus autofluorescence (FAF) characteristics of metastatic choroidal tumors with optical coherence tomography/scanning laser ophthalmoscope (OCT/SLO)**
Natesh S, Chin KJ, Finger PT

17.02–17.10 **Discussion**

Thursday
10th September 2009

Uveal tumours

Session 8

Uveal tumour case reports (2)

Thursday 10th September 2009

Uveal tumours

Session 8

Chairs: P Rundle, E Krema, ER Simpson, Cauchi P

Uveal tumour case reports (2)

17.10–18.00

Multiple pigmented fundus lesion in a Hispanic patient

Manquez ME, Vigorena P, Hepp R, Vines E
Clínica Oftalmológica Luis Pasteur, Santiago, Chile

Choroidal melanoma as the fourth tumor in a single patient

Yarovoy AA, Bulgakova ES
Ocular Oncology Department, S. Fyodorov Eye Microsurgery Complex, Moscow, Russia

Trifocal unilateral choroidal melanoma in a patient with ocular melanocytosis

Parvus BJ, Shields CL
Ocular Oncology Service, Wills Eye Institute, Thomas Jefferson University, Philadelphia, PA, USA

Fundus autofluorescence of diffuse uveal melanocytic proliferation

Semenova EA, Chin KJ, Natesh S, Finger PT
The New York Eye Cancer Center, New York, New York USA

Eviscero-enucleation of the eye with unsuspected uveal melanoma

Yarovoy AA[1], Bulgakova ES[1], Shatskih AV[2]
[1]Ocular Oncology Department, [2]Ocular Pathology Department, S. Fyodorov Eye Microsurgery Complex, Moscow, Russia

Unexpected findings in an eye enucleated after repeat retinal surgery

Loeffler KU, Herwig MC,
Department of Ophthalmology, Division of Ophthalmic Pathology, University of Bonn, Germany

Choroid malignant melanoma growing in the supra choroidal space: ultrasonographic evidence

Mazzeo SV[1], Lodi L[2]
Studio Zavarini, Ferrara[1] and UO Oculistica, Ospedale Maggiore, Bologna[2], Italy

Extrascleral recurrent uveal melanoma

Parrozzani R[1], Alemany-Rubio E[1], Urban F[1], Gurabardhi M[1], Pilotto E[1], Midena E[1,2]
[1]*Department of Ophthalmology, University of Padua, Padua, Italy*
[2]*G.B. Bietti Eye Foundation, IRCCS, Roma, Italy*

Choroidal melanoma recurrence: confocal imaging with a retro-mode scanning laser ophthalmoscope

Pilotto E[1], Parrozzani R[1], Urban F[1], Midena E[1,2]
[1]*Department of Ophthalmology, University of Padua, Padua, Italy*
[2]*Fondazione GB Bietti per l'Oftalmologia, IRCCS, Roma, Italy*

Choroidal metastasis as a primary presentation of non small cell lung cancer

Vishnevskia-Dai V
The Goldschleger Eye Institute, Sheba Medical Center, Tel Aviv University, Israel

An unusual choroidal tumour

Coupland SE, Damato B
School of Cancer Studies, University of Liverpool, Liverpool, UK

'Double Jeopardy'

Horgan N
Royal Victoria Eye and Ear Hospital, Dublin, Ireland

Friday
11th September 2009

Retinal tumours

Session 1

Retinoblastoma

Retinoblastoma - in premature infants

Retinoblastoma - diagnosis

Retinoblastoma - treatment

Friday 11th September 2009

Retinal tumours

Session 1
Chairs: A Moll, L Desjardins, I Dunkel

Retinoblastoma

Retinoblastoma - in premature infants

8.00–8.03 **Retinoblastoma in children born before 40 weeks gestation**

Emerson MV, Huryn LA, Williams BK, Schefler AC, Dunkel IJ, Marr BP, Murray TG, Abramson DH

Retinoblastoma - diagnosis

8.03–8.06 **Role of fluorescein angiography in the management of intra-ocular retinoblastoma**

Munier FL, Gaillard M, Balmer A

8.06–8.09 **Brain abnormalities on MRI in retinoblastoma patients**

Rodjan F, de Graaf P, Moll AC, Imhof SM, Verbeke JIML, Sanchez E, Castelijns JA

8.09–8.12 **Diagnosis of retinoblastoma: how good are referring physicians in 2009?**

Maki JL, Marr BP, Abramson DH

8.12–8.15 **Angiographic findings in Coats' disease**

Ghassemi F, Shields CL, Gorski M, Mashayekhi A, Hartzel K, Shields JA

Retinoblastoma - treatment

8.15–8.20 **Treatment of unilateral retinoblastoma: results of a prospective study in Argentina**

Chantada G, Fandiño A, Guitter M, Raslawski E, Manzitti J, de Davila MTG, Dominguez J, Scopinaro M

8.20–8.25 **Retinoblastoma in Egypt: a 5 year review of unilateral and bilateral cases: clinical spectrum and management**

Othman IS, Ademola-Popoola DS, Shelill A, Zico O

8.25–8.30 **The survival and visual outcome of bilateral retinoblastoma in Taiwan**

Hsueh P-Y, Kao L-Y

8.30–8.35 **Outcomes of A + B tumours – do familial/non-familial eyes behave differently?**

Hitchcott C, Turner S, Cole T, Jenkinson H, Parulekar M, Willshaw H

8.35–8.40 **Eye salvage rate in retinoblastoma: a comparison between the Reese Ellsworth classification and the IIRC classification system**

Khetan V, Sudrik S, Parmar V, Nagpal A, Sharma T, Gopal L, Chandra A

8.40–8.45 **Children's Oncology Group (COG) clinical trials in retinoblastoma: an update from the Children's Oncology Group**

Chintagumpala M, Friedman D, Jubran R, Dunkel I, Chevez-Barrios P, Shields C, Rodriguez C, Meadows A, Murphree L

8.45–8.50 **Japan retinoblastoma group study: novel local chemotherapies can reduce the burden of systemic chemotherapy to achieve eye preservation without EBRT**

Yanagisawa T, Fukuoka K, Suzuki T, Akiyama M, Yuza Y, Yokoi K, Tera-Mikami Y, Kato Y, Uchiyama H, Eto Y, Ida H, Suzuki S, Kaneko A, Nisikawa R

8.50–8.55 **The results of treatment in patients with high risk (HR) retinoblastoma (RB)**

Ushakova T, Dolgopolov I, Gorovtzova O, Mateeva I, Pavlovskaya A, Glekov I, Osipova M, Bolotin M, Pimenov R, Boyarshinov V, Poliakov V, Mentkevich G

8.55–9.00 **Multiple-failure intraocular retinoblastoma can be cured by cyclosporine-modulated chemotherapy with focal cryo/laser therapy**

Chan HSL, Héon E, Dimaras H, Gallie BL

9.00–9.05 **Hypoxic retinoblastoma tumor targeting: use of periocular delivery of 2-deoxy-D-glucose**

Boutrid H, Pina Y, Cebulla CM, Schefler AS, Lampidis TJ, Murray TG

9.05–9.10 **Focal, periocular delivery of 2-deoxy-D-glucose as an adjuvant to chemotherapy for treatment of advanced retinoblastoma: evaluation in a murine transgenic retinoblastoma model**

Murray TG, Boutrid H, Pina Y, Schefler AS, Lampidis TJ, Cebulla CM

9.10–9.15 **Subconjunctival nanoparticle carboplatin in the treatment of murine retinoblastoma**

Grossniklaus HE, Kang SJ, Durairaj C, Kompella UB, O'Brien JM

9.15–9.40 **Discussion**

Friday
11th September 2009

Retinal tumours

Session 2

Retinoblastoma

Retinoblastoma - chemotherapy

Hot topics
– local delivery of chemotherapy

– Intra-arterial melphalan

Keynote lecture

Friday 11th September 2009

Retinal tumours

Session 2

Chairs: D Abramson, T Hadjistilianou, J Hungerford

Retinoblastoma

Retinoblastoma - chemotherapy

Hot topic – local delivery of chemotherapy

9.40–9.43 **Periocular carboplatin for retinoblastoma: toxicity and response with 101 injections**

Marr B, Dunkel IJ, Linker A, Abramson DH

09.43–09.46 **Periocular carboplatin injection in the management of retinoblastoma with diffuse vitreous seeds**

Honavar SG, Shome D, Reddy VA

09.46–09.49 **Periocular carboplatin for retinoblastoma – with or without systemic chemotherapy?**

Parulekar MV, Jenkinson H, Willshaw HE, Hitchcott C, Ainsworth JR, Morland B

09.49–09.52 **Intravitreal methotrexate monotherapy as salvage treatment for recurrent retinoblastoma after standard chemoreduction**

Kivelä T, Eskelin S, Lindahl P, Majander A

Hot topic – intra-arterial melphalan

9.52–9.55 **Our recent modifications of local chemotherapies for preservation of eyes with retinoblastoma**

Kaneko A, Kaneko T, Moori M, Takeuchi S

9.55–9.58 **Success or failure of intra-arterial chemotherapy for retinoblastoma: impact of orbital vascular anatomy**

Marr B, Gobin YP, Abramson DH

9.58–10.01 **Ophthalmic arterial injection therapy for retinoblastoma patients by using melphalan: technique and eye preservation rates**

Yamane T, Suzuki S, Kaneko A, Mohri M

10.01–10.04 **Ocular and systemic prognosis of selective ophthalmic arterial injection for intraocular retinoblastoma**

Suzuki S, Kaneko A

10.04–10.07 **Direct intra-arterial (ophthalmic artery) chemotherapy with melphalan for advanced intraocular retinoblastoma: the Italian experience**

Hadjistilianou D, Venturi C, De Francesco S, Bracco S, Galluzzi P, Motolezi E, Balestri P, Dambrosiou A

10.07–10.10 **ERG monitoring of retinal function after intra-arterial chemotherapy infusion for retinoblastoma**

Brodie SE, Marr B, Gobin YP, Abramson DH

10.10–10.13 **The histopathological evaluation of retinal toxicity in the retinoblastoma eye treated by ophthalmic arterial infusion of melphalan**

Ohshima K, Suzuki S

10.13–10.16 **Systemic (non-ocular) toxicity associated with intra-arterial melphalan chemotherapy: the New York experience**

Dunkel IJ, Gobin YP, Salvaggio K, Marr B, Abramson DH

10.16–10.19 **Evaluation of the radiation exposure of angiography for intra-arterial chemotherapy administration for retinoblastoma**

Mahajan A, Schellingerhout D, Woo SY, Gombos D

10.19–10.22 **Enucleation after treatment with intra-arterial chemotherapy for retinoblastoma: a report on 10 cases**

Jahn CG, Gobin YP, Marr BP, Dunkel IJ, Brodie SE, Bornfeld N, Char DH, Folberg R, Imhof SM, Lin AY, Maki JL, Mesfer SA, Moll AC, Abramson DH

10.22-10.25 **Uncovering the mechanism of action of cardenolides as novel therapeutic agents for retinoblastoma**

Antczak C, Ramirez C, Radu C, Abramson D, Djaballah H

10.25–10.40 **Discussion**

Keynote lecture

10.40–11.00 **The treatment of intraocular retinoblastoma in the Curie Institute in 2009**

Laurence Desjardins
Institute Curie, Paris, France

11.00–11.15 **Coffee and posters**

Friday
11th September 2009

Retinal tumours

Session 3

Retinoblastoma

Retinoblastoma - chemotherapy - toxicity

Retinoblastoma - chemotherapy - clinic model

Retinoblastoma - external beam radiotherapy

Retinoblastoma - histopathology

Retinoblastoma - second tumours

Retinoblastoma - social issues

Friday 11th September 2009

Retinal tumours

Session 3

Chairs: L Lumbroso, J Kingston, T Murray

Retinoblastoma

Retinoblastoma – chemotherapy - toxicity

11.15–11.20 **Carboplatin induced ototoxicity in retinoblastoma patients treated with systemic chemotherapy**

Wilson MW, Qaddoumi I, Bass J, Watkins A, Haik BG, Rodriguez-Galindo C

11.20–11.25 **Pineal gland changes in patients with retinoblastoma treated with systemic chemotherapy**

Wilson MW, Rodriguez-Galindo C, Watkins A, Haik BG, Helton KJ

Retinoblastoma - chemotherapy - clinic model

11.25–11.30 **A multi-center model for the management of retinoblastoma: a virtual RB center**

Gombos DS, Chintagumpala M, Chevez-Barrios P, Zage P, Hurwitz RL, Herzog C, Mahajan A, Woo S

Retinoblastoma - external beam radiotherapy

11.30–11.35 **Ocular outcomes after external beam radiotherapy as second line conservative management of retinoblastoma**

Lumbroso-Le Rouic L, Dendale R, Benesty J, Lévy-Gabriel C, Aerts I, Bours D, Savignoni A, Doz F, Desjardins L

Retinoblastoma - histopathology

11.35–11.40 **Histopathology of retinoblastoma after primary chemotherapy**

Ali MJ, Gupta R, Vemuganti GK, Honavar SG

11.40–11.45 **Retinoblastoma (Rb) in older children: a clinicopathological profile**

Gupta K, Mehta M, Pushker N, Chawla B, Meel R, Bajaj MS, Sen S, Kashyap S, Chandra M, Ghose S

11.45–11.50 **Lack of correlation between the histology and magnetic resonance imaging of the optic nerve in eyes primarily enucleated for retinoblastoma**

Wilson MW, Rodriguez-Galindo C, Billups C, Haik BG, Laningham F, Patay Z

11.50–11.55 **High-risk features and tumor differentiation in retinoblastoma: a retrospective histopathologic study**

Eagle RC Jr

Retinoblastoma - second tumours

11.55–12.00 **Risk of second cancers following treatment for retinoblastoma since 1970**

Kleinerman RA, Sakata R, Abramson DH

12.00–12.05 **Uterine leiomyosarcoma in retinoblastoma: risky enough for prophylactic intervention?**

Francis JH, Kleinerman RA, Abramson DH

Retinoblastoma - social issues

12.05–12.10 **The role of education in the promotion of red reflex assessments and the sensitivity of this test**

Reddy MA, Hindocha M, Price M

12.10–12.15 **Coping strategies of retinoblastoma survivors in relation to behavioural problems**

Van Dijk J, Grootenhuis MA, Imhof SM, Cohen-Kettenis PT, Moll AC, Huisman J

12.15–12.20 **Innovative tools for use with children who have undergone enucleation**

McCalla M, Bellfield J

12.20–12.25 **Are socioeconomic status and ethnicity risk factors for late presentation of retinoblastoma in the UK?**

Bourkiza R, Kingston J, Hungerford JL, Reddy MA

12.25–12.30 **National consensus achieved through the Canadian Retinoblastoma Care Guidelines**

Dimaras H, Weizblit N, Gronsdahl P, Downie RR, Chan HSL, Gallie BL, Lank CN, and the National Retinoblastoma Strategy Group

12.30–12.35 **Long-term retinoblastoma follow-up: with or without general anaesthesia?**

Batra R, Abbott J, Jenkinson H, Ainsworth JR, Kearns P, Parulekar M

12.35–13.00 **Discussion**

13.00–14.00 **Lunch**

Friday
11th September 2009

Retinal tumours

Session 4

Retinoblastoma

Retinoblastoma - genetics
Paradigm shifting
Cell of origin
Conception and testing
Mouse models
Protein and RNA function
Genotype-phenotype

Retinoblastoma - prenatal testing

Other retinal tumours

Stallard lecture

Friday 11th September 2009

Retinal tumours

Session 4

Chairs: S Imhof S, B Gallie, F Munier

Retinoblastoma

Retinoblastoma - genetics

Paradigm shifting

14.00–14.05 **An unexplained mechanism for familial retinoblastoma**

Rosser E, Price K, Price E, Kolkiewicz K, Patel R, Bunyan D, Robinson D, Hungerford J, Onadim Z

14.05–14.10 **A subset of retinoblastoma without RB1 gene mutation shows high level MYCN gene amplification**

Yee S, Rushlow D, Kennett J, Pajovic S, Boutros P, Spencer C, Lam W, Houdayer C, Raizis A, Lohmann D, Gallie BL

14.10–14.15 **Apparent cancer cells not derived from the malignant clone in retinoblastoma tumors**

Chévez-Barrios P, Gombos DS, Wadhwa L, Perlaky L, Bond W, Penland R, Ty MT, Zwaka T, Hurwitz MY, Hurwitz RL

Cell of origin

14.15–14.20 **Origin of human retinoblastoma: using the SD-OCT to determine the retinal layer of origin**

Mallipatna A, Vandenhoven C, Gallie B, Héon E

14.20–14.25 **Retinoblastoma has properties of a cone precursor tumor**

Cobrinik D, Xu XL, Fang Y, Lee TC, Jhanwar SC, Abramson DH

Conception and testing

14.25–14.30 **Are children born after infertility treatment at increased risk of retinoblastoma?**

Foix-L'Hélias L, Lumbroso-Le Rouic L, Marchand L, Aerts I, Gauthier-Villars M, Labrune P, Bouyer J, Doz F, Kaminski M

14.30–14.35 **Higher incidence of retinoblastoma in children born after in vitro fertilization found in the Dutch retinoblastoma register**

Moll AC, Marees T, Dommering ChJ, Imhof SM, Kors WA, Ringens PJ, van Leeuwen FE

Mouse models

14.35–14.40 **Anatomic, histopathologic, and gene expression analysis of metastatic tumors in the $LH_{BETA}T_{AG}$ transgenic mouse model of retinoblastoma**

Schefler AC, Boutrid H, Padgett KR, Nathanson L, Pina Y, Hernandez E, Dubovy SR, Murray TG

14.40–14.45 **Retinoblastoma tumor burden: effect of macrophage depletion on $LH_{BETA}T_{AG}$ retinal tumor growth**

Pina Y, Boutrid H, Cebulla CM, Schefler AS, Jockovich ME, Alegret A, Jager MJ, Ly LV, Murray TG

Protein and RNA function

14.45–14.50 **Comparison of the protein profile in human retinoblastoma tumor and seeding**

Vorum H, Ludvigsen M, Honoré B, Abramson DH, Urbak SF

14.50–14.55 **TGF-β1, TGF-β TYPE 2 receptor, survivin and HLA Class II expressions in retinoblastoma**

Kiratli H, Erdogan-Poyrac C, Soylemezoiglu F

14.55–15.00 **The miR-17-92 gene is amplified and over expressed in retinoblastoma**

Biewald E, Stephan H, Mestdagh P, Schulte JH, Schramm A, Eggert A, Bornfeld N

Genotype-phenotype

15.00–15.05 **RB1-mutations, second primary malignancies and hereditary retinoblastoma**

Marees T, Dommering CJ, van der Hout AH, Imhof SM, Ringens PJ, van Leeuwen FE, Moll AC

Retinoblastoma - prenatal testing

15.05–15.10 **Role of linkage analysis in excluding risk for siblings and cousins in familial retinoblastoma**

Cole T, Parulekar M, Jenkinson H, O'Grady A, Ainsworth JR, Willshaw HE

15.10–15.15 **The uptake of prenatal testing for retinoblastoma susceptibility by pregnant women at increased risk**

Dommering CJ, van der Hout AH, Moll AC, Imhof SM, Meijers-Heijboer EJ

Other retinal tumours

15.15–15.18 **Combined hamartoma of the retina and retinal pigment epithelium in 77 consecutive patients**

Pirondini C, Thangappan A, Hartzell K, Valente P, Shields CL, Shields JA

15.18–15.21 **Focal pseudoneoplastic retinal gliosis: a new clinical entity?**

Shields JA, Bianciotto C, Shields CL

15.21–15.40 **Discussion**

Stallard lecture

15.40–16.00 **Super selective intrarterial chemotherapy for retinoblastoma: why, how and wow!**

David Abramson
Memorial Sloan-Kettering Cancer Center, New York, NY, USA

16.00–16.15 **Tea and posters**

Friday
11th September 2009

Retinal tumours

Session 5

Retinal tumour case reports

Friday 11th September 2009

Retinal tumours

Session 5

Chairs: J Shields, A Reddy, J Augsburger, Mruthyunjaya P

Retinal tumour case reports

16.15–18.00

Fundus finding behind a cataract following trauma in a child

Shields JA, Shields CL
Oncology Service, Wills Eye Institute, Philadelphia PA, USA

Ophthalmic artery infusion chemotherapy for bilateral recurrent retinoblastoma

Augsburger JJ, Correa ZM, Simoes CC
University of Cincinnati College of Medicine, Department of Ophthalmology, Cincinnati, OH, USA

Recurrent retinoblastoma 6 years following ^{106}Ruthenium brachytherapy

Munier FL[1], Möckli R[2], Balmer A[1], Hadjistilianou T[3],
[1]Hôpital Jules Gonin, and [2]Service de Radio-Oncologie, CHUV, Lausanne, Switzerland, [3]Ocular Oncology Unit, University of Siena, Siena, Italy

Supraselective intra-arterial melphalan infusion: evaluation of orbital and ophthalmic vasculature alterations

Murray TG, Boutrid H, Wolfe SQ, Schefler AS, Pina Y, Moftakhar R, Fernandes CE, Reichbach J, Aziz HA, Marcus D, Aziz-Sultan MA
Bascom Palmer Eye Institute, Miami, FL, USA

Severe aseptic orbital cellulitis with subtenon carboplatin for intraocular retinoblastoma

Shah PK, Narendran V, Kalpana N
Department of Pediatric Retina, Aravind Eye Hospital, Coimbatore, India

Giant orbital retinoblastoma: a case report

Hadjistilianou T[1], Borri M[1], De Francesco S[1], De Luca M[1], Menicacci F[1], Galluzzi P[2], Toti P[3], Dambrosio G[4]
[1]Unit of Ophthalmology and Ocular Oncology, University of Siena, Italy
[2]Unit of Neuroradiology, Policlinico LE SCOTTE, Siena, Italy
[3]Deparment of Pathology, University of Siena, Italy
[4]Department of Pediatrics, University of Siena, Italy

13qdel syndrome and corpus callosum agenesis in two identical twins

Hadjistilianou T[1], De Francesco S[1], De Luca M[1], Borri M[1], Renieri A[2], Mari F[2], Venturi C[3], Bracco S[3], Munier F[4]
[1]*Retinoblastoma Referral Center, University of Siena, Italy*
[2]*Unit of Genetics, University of Siena, Italy*
[3]*Unit of Neuroradiology, Policlinico Le Scotte, Siena, Italy*
[4]*Hopital Jules Gonin, Lausanne, Switzerland*

Retinoblastoma gone sour

Shields CL
Ocular Oncology Service, Wills Eye Institute, Philadelphia, PA, USA

Anterior diffuse retinoblastoma: mutational analysis and immunofluorescence staining

Grossniklaus HE, Crosby M, Hubbard GB, Gallie B
Emory University, Atlanta, Georgia, USA

Bilateral central retinal artery occlusion in a patient with primary CNS lymphoma

Gregory ME, Chadha V, Roberts F, Kemp E, Cauchi P
Tennent Institute of Ophthalmology, Glasgow, UK

Trilateral retinoblastoma primary treated as a PNET

Hautz W, Gralek M, Rutynowska O, Dembowska-Baginska B, Chipczynska B, Cieslik K
The Children's Memorial Health Institute, Warsaw, Poland

A lady with lymphoma and elevated human chorionic gonadotropin

Abramson DH, Marr BP
Memorial Sloan-Kettering Cancer Center, New York, NY, USA

Vitelliform lesion outside the posterior pole: how a mystery case in 2007 became no longer a mystery in 2007…

Grange JD, Gain P, Zech C, Tran Manh Sunh R, Grivet D
Lyon and Saint -Etienne University Eye Clinics, France

Primary ciliary body astrocytic hamartoma in tuberous sclerosis complex: case report

Khetan V[1], Parmar V[1], Sudrik S[1], Krishnakumar S[2], Lingam Gopal L[1]
[1]*Department of Vitreoretina and Ocular Oncology, Medical Research Foundation, Sankara Nethralaya, Chennai, India*
[2]*Department of Ocular Pathology, Medical Research Foundation, Sankara Nethralaya, Chennai, India*

Enlargement of retinal astrocytic hamartomas in a patient with tuberous sclerosis

Kodama T, Yoshizako H, Ohira A
Department of Ophthalmology, Faculty of Medicine, Shimane University, Japan

A retinal astrocytic hamartoma with vitreous hemorrhage

Lally SE, Shields CL, Shields JA
Oncology Service, Wills Eye Institute, Philadelphia PA, USA

Spontaneous vitreous hemorrhage in patients with tuberous sclerosis – report of 2 cases

Simoes CC, Correa ZM, Augsburger JJ
University of Cincinnati College of Medicine, Department of Ophthalmology, USA

Aggressive retinal astrocytoma associated with tuberous sclerosis complex managed with brachytherapy

Drummond SR, Kemp EG
Tennent Institute of Ophthalmology, Gartnavel General Hospital, Glasgow, UK

Acquired retinal astrocytoma managed with endo-resection

Vilaplana D, Castilla M, Poposki V, Alameda F, Shields CL
Hospital Universitari de l'Esperanza, Barcelona, Catalonia, Spain

Eleven-year-old with optic nerve head lesion

McCannel CA
Jules Stein Eye Institute, UCLA, Los Angeles, CA, USA

Retinal metastases from small cell lung carcinoma: report of 2 cases

Novak Andrejčič K[1], Popovič P[1], Vidovič Valentinčič N[1], Globočnik Petrovič M[1], Kloboves Prevodnik V[2]
[1]*University Medical Centre Ljubljana, Department of Ophthalmology, Ljubljana, Slovenia*
[2]*Institute of Oncology, Department of Cytology, Ljubljana, Slovenia*

Juxtapapillary retinal hemangioblastoma

Materin MA, Shields CL
Oncology Service, Wills Eye Institute, Philadelphia, PA, USA

Saturday
12th September 2009

Intraocular lymphoma and TNM

Session 1

Intraocular lymphoma

TNM staging

TNM symposium

Saturday 12th September 2009

Intraocular lymphoma and TNM

Session 1

Chairs: J Pulido, P Finger, S Coupland

Intraocular lymphoma

8.30–8.40 **Intraocular lymphoma in Japan**
Goto H, Kimura K, Usui Y

8.40–8.50 **PIOL: local or systemic therapy?**
Pulido JS

8.50–9.00 **Discussion**

TNM staging

9.00–9.10 **American Joint Committee on Cancer TNM classification for lacrimal-gland adenoid cystic carcinoma is predictive of outcome**
Esmaeli B, Ahmad M, Williams M, Nguyen J, Fay A, Woog J, Selvadurai D, Rootman J, Weis E, Selva D, McNab A, DeAngelis D, Calle A, Lopez A

9.10–9.20 **A TNM-based clinical staging system of ocular adnexal lymphomas**
Coupland SE, White VA, Rootman J, Damato B, Stefan Seregard S, Armitage JO, Finger PT

9.20–9.30 **An eye cancer bio-informatics grid initiative of the AJCC-UICC Ophthalmic Oncology Task Force**
Finger PT, Ainbinder DJ, Coupland SE, Damato B, Edward DP, Fleming JC, Gallie BL, Grossniklaus HE, Harbour JW, Holbach LM, Hungerford JL, Karcioglu ZA, Kivela T, McGowan H, Rootman J, Seregard S, Singh AD, White VA

TNM symposium

This TNM Ocular Tumour Symposium aims to provide a summary of the changes to the AJCC/UICC ocular tumour staging systems, published in the 7th edition in 2009. Considerable alterations have been made since the 6th edition, for example, to uveal and conjunctival melanoma, as well as to retinoblastoma staging.

A novel TNM-based staging system has also been designed for the ocular adnexal lymphomas. These revisions will be presented within the clinical context, enabling a better understanding of the TNM staging systems and the necessity of their use, particularly with respect to the establishment of potential biomarkers for these differing malignant neoplasms.

9.30–11.00 Presentation of the 7th edition of the TNM staging of ocular tumours

Chair: Paul Finger

Choroidal melanoma:	Tero Kivelä
Retinoblastoma:	William Harbour
Ocular adnexal lymphomas:	Sarah Coupland
Conjunctival melanoma:	Stefan Seregard
Eyelid carcinoma:	Leonard Holbach
Lacrimal gland tumours:	Bita Esmaeli
About EyeCancerBIG:	Paul Finger

Abstracts

Wednesday
9th September 2009

Orbital, eyelid and epibulbar tumours

Session 1

Orbital tumours

Trephine biopsy of orbital tumors

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Background
Fine-needle aspiration biopsy of orbital tumors is not able to provide a tissue specimen for histological and immunohistochemical analysis; its diagnostic accuracy depends on tumor tissue solidity and other factors.

Purpose
To evaluate the capabilities and possible complications of orbital tumors biopsy with semi-automated trephines.

Methods
Thirty-two biopsies (29 patients, 32 eyes) were performed using 20- and 18-gauge semi-automated trephines, some of biopsies – under US-guidance. In 16 patients the lesions were located in posterior orbit. An average of 2 punctures in different directions was performed.

Results
Tissue cores were obtained in all cases. Diagnostically sufficient for histological analysis specimens were obtained in 81% of biopsies. Three patients required additional incisional and two excisional biopsy. Twenty tumors were malignant (15 lymphomas, 3 rhabdomyosarcomas, 1 lacrimal gland carcinoma, and 1 breast carcinoma metastasis). There were 3 benign tumors, 5 pseudotumors and 1 orbital fibrosis after 3 previous surgeries. In some cases immunohistochemical analysis was fulfilled. There was only one complication of biopsy procedure – mild retrobulbar hematoma. The causes of biopsy failures were tumor tissue heterogenicity, dense orbital fibrosis and technical errors.

Conclusion
Semi-automated trephine biopsy of orbital mass lesions is a safe procedure which provides a sufficient amount of tissue material for full-bodied histological analysis and has minimum complications. This procedure can be an alternative or addition to fine-needle aspiration biopsy.

Orbital MALT lymphoma versus orbital mantle cell lymphoma

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Background
Among ocular non-Hodgkin's lymphomas, indolent MALT lymphomas predominate. Mantle cell lymphomas are the second most frequent type of small cell lymphomas. It is assumed that nodal mantle cell lymphomas are characterized by the most aggressive clinical course.

Aim
To study characteristic features in the onset, development and course of orbital MALT lymphomas and mantle cell lymphomas.

Materials
During the period from 1983 through 2008, we have studied orbital non-Hodgkin's lymphomas in 43 patients. According to WHO 2001 classification, morphological, immunological and genetic study was conducted to diagnose the type of the lymphomas. MALT lymphomas were diagnosed in 28 patients, while mantle cell lymphomas were found in 10 patients.

Results
Orbital MALT lymphomas have developed more rapidly than mantle cell lymphomas – several months compared to several years. On the whole, the damage of the orbit in MALT lymphomas as compared to mantle cell lymphomas is more severe: the eye mobility restriction developed more often, exophthalmos was of higher degree. IE stage of the disease was revealed in 21 out of 28 patients with MALT lymphomas and in 5 out of 10 patients with mantle cell lymphomas. The observation period after the treatment ranged from 1 to 17 years (42% patients were followed for more than five years). Only 3 patients with primary MALT lymphomas developed local relapses (the damage of the second orbit). In one patient, the disease spread to develop non-ocular relapses. During this period, neither local relapses nor tumor generalization were observed in patients with IE stage mantle cell lymphomas.

Conclusion
Primary MALT lymphomas develop more rapidly, have more severe manifestations and are characterized with a more aggressive course as compared to primary orbital mantle cell lymphomas. Relapses and generalization were observed in patients with MALT lymphomas and chromosome 3 trisomy. Primary orbital mantle cell lymphomas have a more favorable prognosis as compared with nodal mantle cell lymphomas.

Orbital schwannoma: a clinicopathologic study

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Background
To study the clinicopathologic profile of cases of orbital schwannoma.

Methods
Retrospective data analysis of histopathologic record of orbital schwannoma in a tertiary care referral center over a period of 15 years (1993-2008).

Results
Thirty-nine patients were found to have orbital schwannoma on histopathological examination. Age of onset ranged from 8 to 65 years. Schwannoma was more common in females. Clinical details of 4 patients were not available. Protrusion of eye was the commonest presenting symptom in 33 cases followed by swelling of eyelids in 2 cases. Other associated symptoms include diminution of vision in 11 cases and pain in 5 cases. Duration of symptoms ranged from 3 months to 15 years. Fundus examination revealed disc oedema in 11 cases. Ultrasonography and CT scan revealed well defined mass in extraconal space in 26 cases and intraconal space in 9 cases. Cystic cavities were present in 12 cases. Radiologic picture was quite variable resulting in primary diagnosis of combined venous-lymphatic vascular malformation in 10, lacrimal gland tumor in 2, dermoid cyst in 5, hydatid cyst in 2, schwannoma in 16 cases. Histopathologic studies were consistent with features of schwannoma. Cystic degeneration was present in 16 cases.

Conclusion
Schwannomas constituted for 6.5% of all orbital tumor in our series. Cystic degeneration was present in 41% of schwannomas. Histopathologic examination is essential to confirm the diagnosis of a schwannoma that may be otherwise clinically confusing.

Pathogenesis of orbital tumours with clinical implications in Maadi AF Hospital, Cairo

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Understanding the pathogenesis of tumours is not only important in diagnosis, but also in determining the treatment options and anticipating prognosis of different orbital tumours.

The main idea is to highlight that everything in tumour pathogenesis whether increase in cell growth or decrease in cell apoptosis is due to certain kinds of proteins expressed by certain genes. Identification of tumour cells by their surface receptors and variations in tumour behaviour whether aggressiveness or resistance to drugs. All these are also due to various kinds of proteins. Breakdown of the balance between function of proto-oncogenes and that of onco-suppressor genes, or failure of DNA repair mechanism will lead to evolution of tumors.

In Maadi Armed Forces Hospital in Cairo, being a tertiary referral hospital (1000 beds with 32 specialties), we have managed 411 orbital cases over the last 5 years. One hundred and twenty three cases of them (29.9%) were inflammatory, 120 cases (29%) neoplastic, 117 cases (28.4%) were structural lesions whether congenital or acquired, 26 cases (6.2%) vascular, 12 cases (2.9%) were due to atrophy or degenerations and 13 cases (3.1%) were functional.

Cooperation between different specialties in managing orbital diseases is mandatory, and of course according to the nature of the lesion, you – as an orbital surgeon – may ask help and support from colleagues such as the rheumatologist, oncologist, maxillofacial, neurosurgeon, or radiotherapist. A well organized, systematized approach and intervention at the proper time will solve a lot of problems and improve the cure rate of different orbital cases.

Conclusion

Better understanding of tumour pathogenesis and multidisciplinary approach to various orbital diseases will give the best treatment result and raise the medical service standards in our community.

Iodine-125 orbital brachytherapy with a prosthetic implant in situ

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Background
Brachytherapy is the optimal method of irradiating the orbit after enucleation of an eye with a malignant tumour that has a potential to recur. It consists of 6 trains of I-125 seeds placed around the periphery of the orbit, a shorter central train and a metal disc, loaded with seeds, placed beneath the eyelids. The presence of a prosthetic orbital implant requires omission of the central train and adjustment of the activity of the seeds in the anterior orbit, around the prosthesis.

Methods and materials
This is a retrospective review of the technical modifications and outcome of 12 patients treated this way; 6 with retinoblastoma, 5 with malignant melanoma and one with an intraocular rhabdomyosarcoma. The median dose was 35.5 Gy in 73 hours for retinoblastoma and 56 Gy in 141 hours for malignant melanoma. Patients with retinoblastoma and rhabdomyosarcoma received chemotherapy in addition.

Results
The tubes can be placed satisfactorily around the prosthesis. The increased activity in the anterior half of the tubes produced comparable dose distributions. There have been no orbital recurrences, no extrusion of the prosthesis and cosmesis is very satisfactory.

Conclusion
Insertion of a prosthetic implant at the time of enucleation greatly enhances the subsequent cosmetic appearance. This should be encouraged unless there is frank tumour in the orbit. Orbital brachytherapy without the central train continues to give excellent local control. The short treatment time and good cosmesis are added advantages. The patient is spared the expense and inconvenience of removing and replacing the prosthetic implant.

Cyberknife radiotherapy for the treatment of ocular and periocular lymphoma

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Purpose
To evaluate efficacy, patient tolerance and side effects of cyberknife radiotherapy for treatment of ocular and periocular lymphoma.

Background
Standard radiotherapy for ocular lymphoma is delivered over 4 weeks and can produce side effects including retinopathy, dry eye and cataract. Cyberknife radiotherapy is delivered over 1 week and we evaluate its safety and effectiveness for ocular lymphoma.

Methods
Retrospective series of 12 eyes.

Results
Lymphoma location was orbit (n=5), conjunctiva (n=3), choroid (n=2) and retina (n=2). Mean treatment was 5 days. Complete tumor resolution without recurrence over a mean follow up of 15 months was documented in all cases. There was no radiation retinopathy or cataract.

Conclusion
Cyberknife radiotherapy is a safe and effective treatment for ocular lymphoma with minimal side effect.

Orbital exenteration: the Moorfields 25-year experience

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This paper aims to present the Moorfields Eye Hospital (MEH) experience of exenteration over a 25-year period. A retrospective, non-comparative, interventional case series was undertaken. All patients treated at MEH between 1984 and 2009 had their case notes reviewed for demographics, presenting features, diagnosis, investigations, exenteration subtype, histology, reconstruction, follow-up, outcome and survival. A discussion of the results with special attention to surgical strategies for the differing aetiologies is presented.

Embolisation of distensible venous malformations of the orbit (varices) after direct surgical exposure: a preliminary study

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Objective
To evaluate the outcome of a series of orbital distensible venous malformations (OVMs) with embolisation via surgical exposure.

Methods
A 24 months retrospective review of 55 patients with OVM embolisation by GLUBRAN2 (cyanoacrylate glue) following up at one institute.

Results
Fifty-five patients with an age of between 6 and 65 years. Orbital distensible venous malformations showed by the clinical and radiology. Operative approach included lateral orbitotomy, anterior orbitotomy, trans-subconjunctival and percutaneous puncture. The OVM was embolised by using cyanoacrylate glue. 60% of patients showed complete resolution of symptoms and signs and 40% patients marked improvement following surgery with follow-up 5–25 months.

Conclusion
The embolisation after direct surgical exposure is the safe and effective treatment for OVM. The authors describe their clinical and radiologic features and report a new technique of management for selected cases. This method of embolisation of lesions may greatly resolve the symptoms and cure the enophthalmos.

Angiolymphoid hyperplasia with eosinophilia of the orbit: clinical presentation and treatment results of a rare disease in four patients

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Background
Angiolymphoid hyperplasia with eosinophilia is a rare tumour of the orbit. Various treatments have been recommended including complete surgical excision, surgical debulking, steroid therapy, and irradiation.

Materials and methods
To report four cases of orbital angiolymphoid hyperplasia with eosinophilia including one child and report the sequelae of a) surgical debulking and steroid therapy, b) complete surgical excision, and c) irradiation in one cases.

Results
Cure was achieved in two cases using high dose steroid therapy following surgical debulking and in one case by complete surgical excision. Radiation was performed in one case causing severe necrosis of the entire orbit necessitating orbital exenteration.

Conclusion
We recommend treatment of angiolymphoid hyperplasia with eosinophilia by complete surgical excision where possible or debulking combined with high dose steroid therapy. In our experience radiation should be used with great caution in this disease.

Wednesday
9th September 2009

Orbital, eyelid and epibulbar tumours

Session 2

Orbital tumour case reports

Wednesday
9th September 2009

Orbital, eyelid and epibulbar tumours

Session 3

Eyelid tumours

Infundibulocystic basal cell carcinoma of the eyelid in basal cell nevus syndrome

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Purpose
To describe the histopathological findings in a series of eyelid basal cell carcinomas removed from patients with basal cell nevus syndrome (BCNS).

Methods
Retrospective case series of five patients with BCNS identified from our oculoplastics service. The systemic and ophthalmic features were reviewed, and a retrospective histopathological analysis of all available previously excised eyelid lesions was performed. The pertinent published literature on BCNS and eyelid basal cell carcinoma was reviewed.

Results
A total of 26 eyelid lesions were examined histopathologically. Twenty-three of these lesions were basal cell carcinomas. The infundibulocystic variant of basal cell carcinoma was identified most commonly (57%).

Conclusion
Eyelid basal cell carcinomas in patients with BCNS were commonly of the infundibulocystic variety in our series. Infundibulocystic basal cell carcinomas, which can be clinically indistinguishable from the more common forms, are thought to be less aggressive than other types of basal cell carcinoma and are a reassuring histopathological diagnosis. It is important for the ophthalmologist and pathologist to be aware of infundibulocystic basal cell carcinomas as they are more common in patients with BCNS, and may be a clue to the diagnosis of this autosomal dominant cancer-predisposition syndrome, or other associated syndromes. To our knowledge, this variant of basal cell carcinoma has not been previously discussed in the ophthalmic literature.

Basal cell carcinoma of eyelid skin can be induced by enhanced DNA polymerase iota activity

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Background
Basal cell skin carcinoma (BCC) is one of the most prevalent cancer types. It is known that in patients with Xeroderma pigmentosum (XPV syndrome), BCC often develops. The cause of the XPV syndrome is the damage in the DNA polymerase eta encoding gene. It is the only enzyme responsible for correct thymine dimers penetration in the process of DNA replication in human cells. Its mutant forms are not capable to penetrate thymine dimers that originate from UV irradiation. If DNA polymerase eta is absent or if this enzyme is not active, its function is affected by DNA polymerase iota. Recent studies show that DNA polymerase iota is the main cause for increased mutagenesis in cell of patients with XPV phenotype.

Aim
To assess the activity of DNA polymerase iota in crude extracts of skin BCC without XPV syndrome.

Materials
12 patients with eyelid skin BCC were studied. The control group included 12 patients with benign eyelid neoplasm. DNA polymerase iota – in defiance of Watson-Crick rule – can build G opposite to T matrix to the growing DNA chain even in the presence of dATP excess. To assess the activity of DNA polymerase iota, the reaction of primer construction in an oligonucleotide substrate with subsequent electrophoresis analysis of reaction products was applied. As activators, Mn^{2+} and Mg^{2+} ions were used.

Results
Mn^{2+} activated DNA polymerase iota to a higher degree as compared with Mg^{2+}. Adding of Mn^{2+} caused a three-fold increase in the activity of DNA polymerase iota in skin BCC extracts in comparison to benign neoplasm extracts.

Conclusion
DNA polymerase can play a significant role in the development of skin BCC as its activity (in contrast to other polymerase activity) in this tumor type is extremely increased.

Spectrum of CD30+ lymphoid proliferations in the eyelid

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Background
To report the clinicopathologic features of three patients with CD30+ lymphoproliferations of the eyelid.

Methods
Three patients with CD30+ non-mycosis fungoides T cell lymphoid infiltrates of the eyelid were identified. The histories, clinical findings, pathologic features including immunohistochemical staining, treatments and outcomes were reviewed and compared.

Results
The patients included an 81-year-old man, an 18-year-old man, and a 42-year-old woman, with CD30+ lymphoid proliferations of the eyelid and adjacent soft tissue. The first patient had an isolated crateriform eyelid lesion that was classified as lymphomatoid papulosis (LyP). The second patient had an isolated multinodular lesion of the eyelid that was classified as cutaneous anaplastic large cell lymphoma (cALCL). The third patient presented with eyelid edema with an underlying mass and was found to have widely disseminated anaplastic large cell lymphoma (ALCL).

Conclusion
CD30+ lymphoid proliferations in the eyelid represent a spectrum of conditions ranging from indolent LyP, to moderately aggressive cALCL to highly aggressive ALCL. Clinical examination in patients with CD30+ lymphoid proliferations is necessary to accurately interpret the pathologic findings and diagnose the proliferation as LyP, cALCL or ALCL.

Newly classified EBV positive diffuse large B-cell lymphoma of the elderly in the eyelid and orbit

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Introduction
EBV positive diffuse large B-cell lymphoma of the elderly (EBV+DLBCL-E) is a rare tumor, which was newly classified by the new WHO lymphoma classification in September 2008.

Method
Single case report.

Results
An 83-year-old HIV-negative woman presented with a left-sided eyelid tumor. Magnetic resonance imaging scans revealed the tumor invading left orbit and anterior ethmoid sinus. A subsequent biopsy of the tumor showed EBV+DLBCL-E, with Hodgkinoid and Reed-Sternberg-like cells, expressing CD20, CD30, Pax-5, M UM1, and LMP-1, but not CD5, CD10, bcl-6, or EBNA-2. Positron emission tomography confirmed marked orbital activity and also showed radiopharmaceutical uptake in affected lymph nodes and the posterior extremity of the spleen. She was treated with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone), followed by R-VP16 therapy due to side effecst and achieved a complete remission.

Conclusion
EBV+DLBCL-E should be considered in the differential diagnosis of a lid or orbital tumor of the elderly. To the authors' knowledge, this is the first case of EBV+DLBCL-E in the eyelid and orbit.

Non-surgical treatment for eyelid tumors

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Background
Surgical treatment has been the elective and effective method for the treatment of eyelid tumors with a cure rate of 96%. However, medical treatment could be significantly important in a near future to deal with this pathology and in, special cases, with unexpected cure rates.

Methods
Between November 2003 and November 2008 64 patients with eyelid tumors were treated with intra-lesional Interferon alpha 2b (Intron® Shering Plough). The lesions were documented photographically. The tumors were incisional biopsy proven and there were 50 basal cell carcinomas, 6 recurrent basal cell carcinomas, and 8 squamous cell carcinomas. The patients had hepatic and blood tests and there was up to 60 months follow-up.

Results
There was histologic confirmation of absence of malignant cells two weeks after the end of treatment.

Conclusion
There was complete clinical and histopathology regression of the tumor cells. Apoptosis appeared to be the mechanism of tumor cell death cell tumor and interaction between CD95 and CD95L was related to tumor cell regression.

High-dose-rate interstitial brachytherapy as an alternative to exenteration in recurrent squamous cell carcinoma of the eyelid

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Background
To evaluate the outcome of high-dose-rate (HDR) brachytherapy in the treatment of recurrent squamous call carcinoma of the eyelid in an elderly patient post excision and external beam radiotherapy (EBRT).

Materials and methods
A 79 year old male patient with recurrent squamous cell carcinoma of the eyelid, post excision and EBRT was treated with interstitial brachytherapy. HDR brachytherapy surface mould with Iridium 192 source delivering 35 Gy in 10 fractions using 2 tubes, 2 fractions per day was employed.

Results
The implantation and treatment were uneventful except for epidermal sloughing after a few days which healed. At the end of four months after treatment the patient is disease free.

Conclusion
HRD brachytherapy can be useful in patients with eyelid tumors. It can be considered in recurrent tumors, old and debilitating patients, those who refuse further surgery in the form of exenteration etc. The result in this patient is encouraging and is one of the first few reports from the Indian subcontinent.

Wednesday
9th September 2009

Orbital, eyelid and epibulbar tumours

Session 4

Epibulbar tumours

The differential diagnosis of localised amelanotic limbal lesions: a review of 171 consecutive excisions

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Purpose
To report the distribution of histopathological diagnoses in patients who undergo limbal excision for presumed ocular surface intraepithelial neoplasia.

Design
Clinicopathological case series.

Participants
171 consecutive patients of a single ocular oncologist (JM) underwent excisional biopsy between 1999 and 2009 for a limbal lesion that was clinically suspected to be intraepithelial neoplasia.

Methods
Retrospective review of histopathological reports. To ensure consistency a single pathologist (TD) reviewed all specimens.

Main outcome measure
Histopathological diagnosis.

Results
The population comprised of 128 males and 43 females. The mean age was 63.3 ±15.2 (range: 27–90). 140 (81.4%) lesions were identified as intraepithelial neoplasia (CIN), of which 32 (18.6%) were CIN I, 31 (18.0%) were CIN II, and 77 (44.8%) were CIN III / squamous cell carcinoma (SCC) in-situ. In 7 (4.1%) cases the lesion was SCC. In 2 (1.2%) cases the lesion was amelanotic malignant melonoma. In 27 (15.7%) cases histopathology revealed a benign entity including lesions described as pingueculum, pterygium, granuloma and squamous papilloma, or lesions with non-specific inflammation, epithelial hyperplasia, cellular atypia or keratosis but without dysplasia.

Conclusion
The clinical diagnosis of CIN was accurate in 81.4% of cases. Invasive malignant lesions were identified in 5.3%. This study highlights the importance of acquiring a clinical diagnosis before administering a topical chemotherapeutic to treat an amelanotic limbal lesion.

Conjunctival tumors in a Hispanic population: clinical series of 100 patients from Chile

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Background
Scientific literature displays thousands of papers about conjunctival tumors based on a Caucasian population. Conjunctival tumors are affected by the race of the patients. The higher incidence of squamous cell carcinoma and conjunctival melanoma in white patients is well known, but what happens with Hispanic patients? This series presents 3 years experience in an ocular oncology referral center in Chile.

Purpose
To describe a series of conjunctival tumors in Hispanic population.

Methods
Clinical follow up in 100 consecutive patients sent to a referral center in Chile from April 2006 to April 2009.

Results
Of the 100 Hispanic patients 90% were adults, there was no difference by sex. 67% of lesions were benign, mostly conjunctival nevi. Malignant lesions comprised 33% of the series, including squamous cell carcinoma, melanoma, lymphoma, and sebaceous carcinoma. Melanocytic lesions made up 71% and non-melanocytic lesions 29% of the series.

Conclusion
The conjunctival tumors are present in Hispanic patients from different ages. Most of the tumors are benign lesions. The presence of malignant tumors is this race is not an exception.

Conjunctival melanoma: the major role of primary acquired melanosis in local recurrences and metastatic disease

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Background
The aim of conjunctival melanoma treatment is to eradicate the tumour; to prevent local recurrences, metastatic disease and death; but the therapeutic strategy is not yet clearly codified and remains controversial.

Methods
Retrospective review of the charts of patients treated in our institution for their first localisation of conjunctival melanoma from 2000 to 2007 in order to identify the main clinical and histological prognostic factors for local recurrences and metastatic disease.

Results
Series of 88 patients, 43 had an associated primary acquired melanosis (PAM), 20 originated from a naevus and 25 were de novo. All patients had a surgical excision, 82 % had additional radiotherapy. The median follow up is 45 months. The 5 years survival without metastasis is 88% +/-0.04 and the 5 years survival without local recurrence 72% +/-0.06. In univariate analysis, the determining prognostic factors for survival without recurrence are associated PAM ($p=0.0001$), age ($p=0.002$) and tumor location ($p=0.04$), the determining factors for survival without metastasis are also associated PAM ($p=0.007$), mitotic index ($p=0.007$), tumor location and thickness ($p=0.04$). In multivariate analysis, the only factor with a statistical influence on the local recurrence risk and the metastatic disease risk is a PAM (risk multiplied by 5.3).

Conclusion
Association of PAM with conjunctival melanoma is a major risk factor for local recurrence and metastatic disease. In this context, it is likely that the therapeutic strategy must be adapted. The value of an early exenteration, treatment of PAM with topical Mitomycin and sentinel lymph node biopsy are still to be proven.

Ultrasound biomicroscopic observation of conjunctival melanoma

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Objective
To assess the value of ultrasound biomicroscopy (UBM) in diagnosing conjunctiva melanoma.

Method
Three cases of suspected conjunctival melanoma underwent ophthalmic slit lamp examination and UBM examination pre-operatively. The findings were reported herein. Diagnoses were later confirmed by histopathological results.

Results
Conjunctival melanoma demonstrated as a region of uniformly low reflectivity in UBM images, which was easy to discern from the sclera with high reflectivity. This imaging characteristic was in keeping with its histopathologic features.

Conclusion
UBM can supply information on the depth of conjunctival melanoma and its relationship with the underlying sclera. It aids in distinguishing conjunctival melanoma from choroidal or ciliary tumors with external involvement and also from scleral staphyloma. UBM is a preferable imaging examination for clinical assessment of conjunctival melanoma.

Sentinel lymph node biopsy in the management of conjunctival melanoma

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Background
Sentinel lymph node biopsy (SLNB) is routinely used to stage cutaneous melanoma. However, it is rarely used in conjunctival melanoma. SLNB for conjunctival melanoma was introduced to our service when a survival advantage could be demonstrated for patients with cutaneous melanoma who underwent early treatment of micro-metastases. The aim of this study is to determine the incidence of regional micro-metastases in patients with conjunctival melanoma.

Methods
Patients suffering primary conjunctival melanoma with a tumour thickness of greater than 1.0mm were selected for SLNB. SLNB was undertaken as a secondary procedure following histopathological confirmation of melanoma at excision biopsy (VC, JLH). 9–10 MBq of ^{99m}Tc nanocolloid (in 0.1–0.2ml) was injected into the conjunctival scar. After 30–45 minutes, images were acquired in anterior oblique projections using the LEAP collimator. Following local conjunctival injection of methylene blue, SLNB with gamma probe localisation was performed (VC, GM).

Results
Between May 2008 and April 2009, 8 patients (age range 11–72 years, male to female ratio 1:1) underwent SLNB. On imaging, foci were identified in 6 of 8 patients, however the gamma probe identified radioactivity in all patients. Up to 2 preauricular or submandibular nodes were removed per patient. No surgical complications were encountered. 2 of 8 (25%) patients had positive micro-metastases, one of whom developed widespread metastases and died.

Conclusion
SLNB provides valuable information for patients with conjunctival melanoma. It not only guides subsequent adjuvant therapy but also provides prognostic information that may alter the subsequent management of local disease.

Sentinel lymph node biopsy for conjunctival and eyelid melanoma: experience in 30 patients

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Background
To report the findings on sentinel lymph node biopsy (SLNB) and the correlation with outcomes in 30 patients with ocular adnexal (conjunctival or eyelid) melanomas.

Patients and methods
30 consecutive patients with diagnosis of eyelid or conjunctival melanoma who underwent SLNB at our center between December 2000 and July 2008 are the subject of this report. SLNB was performed as previously described by our group, and patients were prospectively followed. Main outcome measures included findings on preoperative lymphoscintigraphy, SLNB and histopathologic examination of the primary tumor and SLNs and nodal recurrence after SLNB.

Results
Tumor sites were as follows: bulbar conjunctiva only, 14 patients; palpebral conjunctiva only, 8 patients; both bulbar and palpebral conjunctiva, 4 patients; and eyelid skin only, 4 patients. At least 1 SLN was identified in all patients. The median number of SLNs removed was 2 (range 1–5). The most common basin sampled was the intraparotid (16 patients), followed by submandibular (level I) (11 patients), preauricular (9 patients), and superior cervical (level II) (6 patients). Five patients had SLN metastasis. Among the 25 patients with negative SLNB finding, there were two false negative events. There were no false negative events among patients treated during the last 4.5 years of the study. The mean Breslow thickness was 2.57mm (range 0.62–12mm) among patients with negative SLNB and 4.86mm (range 2.0–7.2mm) among patients with positive SLNB findings ($p=0.055$). Ulceration was present in 11 patients (39%), 4 (80%) of 5 patients with positive SLNB findings, and 7 (28%) of 25 with negative SLNB findings including both patients with false-negative results. The median time from SLNB to last contact was 2 years (range 4 months–6 years).

Conclusion
SLNB is safe and effective for identifying nodal micro-metastasis in patients with ocular adnexal melanoma and provides important prognostic information. The false-negative event rate in our series improved in the last 4 years, most likely due to a better technique and better patient selection for SLNB. We recommend consideration of SLNB for patients with intermediate-thickness ocular adnexal melanoma and those with ulceration.

Strontium-90 beta radiotherapy for the adjuvant treatment of conjunctival melanoma

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Background
Incompletely excised conjunctival melanoma can be managed with local radiotherapy, topical chemotherapy or cryotherapy to the surgical margin.

Aim
To report the success of Sr-90 beta radiotherapy for the adjuvant treatment of conjunctival melanoma.

Methods
A retrospective cohort study was undertaken from 1999 to 2007 on all patients who underwent Sr90 beta radiotherapy for incompletely excised conjunctival melanoma. The clinical indication for postoperative beta radiotherapy was histopathological confirmation of conjunctival melanoma at the deep surgical margin. The tumour location, size and associated ocular diagnosis were recorded. Patients were monitored for local tumour control and side effects of treatment. Local control was defined by lack of recurrent conjunctival melanoma at the same site.

Results
Over 8 years, 20 patients underwent Sr-90 beta radiotherapy. All patients had bulbar conjunctival melanoma. The underlying diagnosis was PAM with atypia in 12 of 20 (60%) patients. 9 of 20 (45%) patients had conjunctival melanoma with a thickness greater than 1mm.

Following beta radiotherapy, local control was achieved in 18 of 20 (90%) patients. The median follow up interval was 36 months (range 21 to 51 months). The only side effect from treatment was dry eye in 4 of 20 (20%) patients. No patients suffered limbal stem cell failure, loss of vision or required cataract surgery.

Conclusion
Sr-90 beta radiotherapy is effective in the local control of conjunctival melanoma when incompletely excised from the deep margin of the bulbar conjunctiva. Side effects are limited to dry eye.

Pre-operative exfoliative cytology versus histopathology of squamous cell carcinoma of the conjunctiva and cornea

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Background
Ocular surface squamous neoplasia (OSSN) is the most common conjunctival tumor in adults. The clinical diagnosis of OSSN has to be confirmed pathologically, through cytologic or histopathologic evaluation of tissue. The aim of our study was to determine the reliability of conjunctival exfoliative in predicting the final histopathologic diagnosis of tissue biopsied for ocular surface OSSN.

Methods
Medical records of 49 patients with clinically suspected OSSN whom underwent either conjunctival scrapings (N=36) and/or conjunctival biopsies (N=35) were evaluated. All histological smears were reviewed by 3 pathologists in a blind fashion.

Results
Evaluation of scrapings revealed 91% concordance in interpretation of conjunctival cytologic material as “no dysplasia” vs. “dysplasia”. The concordance dropped to 59% in grading the degree of dysplasia. Evaluation of subsequent biopsy revealed 98% concordance between the pathologists in interpretation of biopsied tissue as “no dysplasia” vs. “any degree of dysplasia”. The concordance decreased to 83% in grading the degree of dysplasia. Cytologic evaluation was capable of distinguishing a neoplastic from non-neoplastic process in 80% of cases.

Conclusion
Ocular surface exfoliative cytology is a simple, safe and relatively non-invasive diagnostic tool. The technique was especially helpful to determine dysplasia prior to surgery and in the setting of recurrent tumors and in follow-up care of patients on topical chemotherapeutic agents. This study suggests that while cytological smears cannot replace an excisional biopsy, but outpatient cytology can play an important role in the diagnosis and management of patients with ocular surface squamous neoplasia.

The use of 1% toluidine blue eye drops in the diagnosis of ocular surface squamous neoplasia

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Purpose
The purpose of this study is to evaluate the use of in vivo toluidine blue stain in the diagnosis of ocular surface squamous neoplasia (OSSN) and correlate the intensity of the stain with the pathological diagnosis.

Methods
A prospective study was performed, at the Ocular Oncology Unit of the Federal University of Sao Paulo, Brazil. Patients with conjunctival non pigmented lesions were submitted to clinical evaluation by slit lamp with and without 1% toluidine blue eye drops and photo documentation. Before the instillation of the dye, proxymetacaine chlorhydrate 1% was used. The patients were grouped according to the clinical aspects of the lesions into 3 groups: Group 1 – patients with OSSN (conjunctival intraepithelial neoplasia and conjunctival squamous cell carcinoma); Group 2 – patients with premalignant lesions (actinic keratosis) and Group 3 – patients with pterygium. All patients were submitted to surgery and the pathology confirmed the diagnosis. The digital images were analyzed by two masked examiners, who had no previous access to the histopathological results. The photos were classified according to the positivity and intensity of the stain. The intensity was classified into dark royal blue, pale royal blue or mixed pattern. Statistical analysis was performed.

Results
Forty-seven patients were included in the study. They were divided into 3 groups according to the histopathological diagnosis: 10 patients had benign lesions (pterygium), 10 patients had pre-malignant lesions (actinic keratosis) and 27 patients had malignant lesions (CIN and SCC). Agreement between observers regarding the analysis of the digital photographs for positivity and intensity of the stain was 82.9% (Kappa 0.938). All patients with malignant lesions had a positive stain by the 1% toluidine blue. One patient had a positive stain but the pathology revealed a benign lesion (false-positive). The statistical analysis showed a sensitivity of 100%, a specificity of 90%, a positive predictive value of 96.4% and negative predictive value of 100%, for the diagnosis of conjunctival malignant lesions with this method, with a statistical significance by the Fisher's exact test ($p<0.0001$). We did not find a correlation between intensity of the stain and histopathological diagnosis (Spearman $r=-0.1125$; $p=0.6783$).

Conclusion
The use of 1% toluidine blue eye drops is an efficient method for the clinical diagnosis of OSSN. Nevertheless, the intensity of the stain is not correlated to the degree of malignancy of these tumors.

Surgery and additional proton therapy for treatment of invasive and recurrent squamous cell carcinomas: technique and preliminary results

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Background
To present the technique and the preliminary results of associating treatment with surgery and proton beam radiotherapy for recurrent and invasive squamous cell carcinomas (SCC).

Materials and methods
From June 2001 to September 2008, fifteen patients were treated in our ocular oncologic centre, for SCC either with recurrences or with invaded resection margins. The treatment combined new surgical resection with proton therapy. A specific device has been made in Nice Cyclotron to carve the proton beam in order to treat the thickness of both the whole lesion site and the adjacent conjunctiva as well as to spare the surrounding healthy structures.

Results
Our patients included 12 males (80%) and 3 females (20%), the mean age was 64 years. 7 cases were T4, 4 cases T3 and 4 T2. The mean follow up was 39 months (range 6–90 months). We have obtained local tumor control for 13 patients (86.8%), recurrences for 2 patients (13.2%). One of them has presented with cervical node metastases. No patients developed recurrences with additional proton therapy performed within 6 months after initial surgical resection. Concerning side effects, 7 patients suffered from sicca-syndrome, 5 needed cataract surgeries, 2 presented with conjunctival post radiation dysplasias, 2 with dilated episcleral vessels, 2 with eyelash loss, one with stenosis of the lacrimal duct and one with glaucoma.

Conclusion
Traditional adjuvant treatments often failed to control recurring and invasive SCC. The preliminary results of the present study suggest that proton therapy may be considered as a good alternative to traditional treatments with acceptable side effects.

The treatment of squamous cell carcinoma of the conjunctiva with excision and beta irradiation

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Background
The incidence of squamous cell carcinoma is increasing as a result of the AIDS pandemic. The most effective treatment is not known. Incomplete surgical excision is often complicated by recurrence. This study reports the results of excision and beta plaque therapy in the treatment of carcinoma-in-situ (CIN) and squamous cell carcinoma (SQ CA) from 1982 to 2008 in South Africa.

Methods
This is a retrospective analysis of 61 patients with CIN and SQ CA followed for more than 2 months after completing beta plaque irradiation. Treatment consisted of excision followed by 4 weekly applications of a Strontium 90 applicator to deliver a total dosage of 60Gy. No tumours were larger than 12mm.

Results
42% of patients were HIV^+. The median follow-up was 16 months (range 2–127 months). SQ CA was diagnosed in 38 patients (62%). Twenty-six lesions (42%) were incompletely excised, and margin involvement could not be determined in 10 (12%). Overall 6 tumours (9.8%) recurred, all of which were from incompletely excised tumours. The recurrence for incompletely excised tumours was 23%. Four of the recurrences occurred in patients with SQ CA. One patient developed scleral thinning. No eyes were enucleated. Recurrences occurred within a median of 5 months after treatment (range 2–40 months).

Conclusion
Beta plaque is a safe effective treatment for CIN and SQ CA and compares favourably with other treatment modalities.

The use of 5-Fluorouracil in the treatment of ocular surface squamous neoplasia

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Purpose
To report the outcome of treatment of ocular surface squamous neoplasia (OSSN) where topical 5-Fluorouracil (5FU) has been used.

Design
Prospective, non-comparative interventional case series.

Participants
62 primary or recurrent OSSN lesions treated by a single ocular oncologist over a 10-year period.

Intervention
44 cases of primary localised OSSN and 11 cases of recurrent OSSN were treated with excision, cryotherapy and adjuvant 5FU. Three cases of localised OSSN and 4 case of diffuse OSSN were treated solely with topical 5FU. In all cases the chemotherapeutic regimen was 5FU 1% four times a day for two weeks continuously.

Main outcome measure
(1) recurrence; (2) complications related to chemotherapy.

Results
Median follow-up time was 13.0 months (mean 16.6 ±15.7 months). There were two cases (3.2%) of recurrent or persistent disease, including a single recurrence in the localised OSSN group treated with excision, cryotherapy and 5FU, and a single case of persistent diffuse disease treated with 5FU alone. Thirty-five patients (56%) had local complications secondary to 5FU. Short-term complications included lid toxicity in 32 patients (52%), epiphora in 3 patients (5%) that settled with syringing, and keratopathy in 7 patients (11%). Three patients were unable to complete the course of 5FU because of local toxicity. One patient had late watering that settled with syringing.

Conclusion
The management of OSSN with 5FU is associated with a low rate of local recurrence. Although 5FU frequently results in short-term complications, most commonly lid toxicity, a full course is usually tolerated and serious long-term complications appear uncommon.

Long-term corneal toxicity of topical chemotherapy with 1% 5-Fluoruracil: a confocal microscopy analysis

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Background
Clinical confocal microscopy (CCM) is a technique for obtaining in-vivo high-resolution optical images of human corneal layers. The aim of this study was to evaluate long-term corneal toxicity of topical chemotherapy with 1% 5-Fluoruracil (5-FU) as a sole or adjuvant treatment of ocular surface squamous neoplasia (OSSN).

Methods
Forty-one consecutive cases of OSSN were included in this non-comparative case series. Patients underwent topical chemotherapy with 5-FU four times/day for 4 weeks (one course). Number of 5-FU cycles was based on cytological and clinical findings. CCM (ConfoScan4, Nidek, Gamagori, Japan) was used to check for 5-FU long-term corneal toxicity. Follow-up was longer than 5 years.

Result
Follow-up was 89 ±14 months (range 63–122 months). Twenty-two patients (53.7%) underwent topical 5-FU as a sole treatment, whereas nineteen patients (46.3%) as adjuvant and/or de-bulking therapy. Mean 5-FU cycles were 1.9 (range 1–5 cycles). Three tumors (7.3%) treated with 5-FU alone recurred during follow-up. Recurrences were treated with additional 5-FU courses, with complete tumor eradication. CCM showed no long-term statistically difference between treated eye and fellow (control) eye in: endothelial cells count, pleomorphism and polimegatisms, anterior stroma keratocytes density and activated keratocytes number, sub-basal nerve plexus fibres number, density, beadings and branching and central cornea epithelium thickness and reflectivity ($p>0.05$).

Conclusion
Topical 5-FU, as a sole or surgical combined therapy, must be considered a long-term safe and effective treatment for patients affected by OSSN.

Conjunctival intra-epithelial neoplasia occurring in young patients with asthma

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Background
To describe conjunctival intra-epithelial neoplasia (CIN) occurring in young patients with asthma.

Methods
Retrospective case series: a review of our ocular oncology database identified 11 patients younger than 55 years of age presenting with conjunctival intra-epithelial neoplasia. Of these 11 patients, 7 (64%) were noted to have co-existent asthma.

Results
Seven patients were included in the study (6 males and 1 female). Mean age at presentation was 44 years (range from 36 to 54 years). Five patients showed unilateral disease whilst two were bilateral. Four patients showed local recurrence however there were no cases of metastasis.

Conclusion
Conjunctival intra-epithelial neoplasia typically occurs in older individuals. A number of aetiological factors are implicated in CIN including life-long exposure to ultra-violet light and immunodeficiency states, particularly HIV infection. Asthma is a common condition affecting more than 3.5 million individuals in the UK, and is associated with atopy in approximately 70% of cases. The occurence of CIN, particularly bilateral CIN in younger immunocompetent individuals is very unusual and the presence of asthma in 64% of our patient cohort suggests that atopic asthma may be a further aetiological factor involved in the development of this rare neoplasm.

Photodynamic therapy in combined treatment of conjunctival hemangioma

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Background
Conjunctival hemangioma is a vascular hamartoma that can cause functional and cosmetic defects.

Methods
14 patients, 12–35 years old (10 females and 5 males), with capillary conjunctival hemangiomas were treated by photodynamic therapy combined with liquid nitrogen cryotherapy and surgery. As photosensitizer we were used methylthioninium chloride 0.2%. PDT was performed in between 2 and 3 procedures before and after surgery and cryotherapy.

Results
On the first day after PDT the photochemical reaction with the destruction of vessels was evident. After 15 days there was significant regression of the tumor and total obliteration of new vessels. After 12 months follow-up there were no signs of tumor relapse.

Conclusion
PDT in combination with surgery and liquid nitrogen cryotherapy has highly functional and aesthetic results in the treatment of epibulbar hemangiomas.

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Uveal tumours

Session 5

Uveal tumour case reports (1)

Wednesday
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Orbital, eyelid and epibulbar tumours

Posters

Orbital schwannoma: clinical manifestations and outcome

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Purpose
Orbital schwannoma is the most common benign neurogenic orbital tumour. We present the largest series of orbital schwannomas in the medical literature, describing the clinical spectrum, radiological findings, histopathological features and outcome.

Methods
Retrospective interventional case series.

Results
36 consecutive cases of orbital schwannoma, comprising 5.1% all consecutive orbital tumors biopsied over 10 years (1998 to 2008) were included. The mean patient age was 33 years, with preponderance towards males (2:1). The patients classically presented with proptosis (91.6%) and presence of a mass (36.1%). The commonest location of the lesion was found to be in the anterior orbit (33.3%) with the superomedial quadrant (27.7%) being most predominant. Atypical manifestations included multiple tumors, schwannoma with malignant change and conjunctival location. Tumors were isodense and well defined on CT scan, involving both extraconal and intraconal spaces. Histopathology showed cellular (33%) and cystic (62%) variants, including Antoni-A and Antoni-B patterns. There were no recurrences following complete excision of the lesion. The follow up of the patients was of the duration of 2 months to 4 years with excellent post operative functional and aesthetic results.

Conclusion
Orbital schwannoma is a benign peripheral nerve sheath tumor and can present in various ways. It should be considered in the differential diagnosis of well-defined orbital tumors.

The effect of perilesional injection of interferon-beta against conjunctival malignant melanoma

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Purpose
To determine therapeutic effect of perilesional interferon-beta (IFN-b) injection as the adjuvant therapy of conjunctival malignant melanoma.

Methods
Consecutive 11 patients of conjunctival melanoma treated in Kyushu University Hospital from 1998 to 2008 were enrolled. Five patients were treated initially with local resection (2 cases) or orbital exenteration (3 cases) without interferon therapy. Other 6 patients underwent pre-and post operative perilesional (subconjunctival and cutaneous) injections of IFN-b. Disease-free survivals curves were generated by Kaplan-Meyer method, and log-rank test was used for comparing these two groups.

Result
In the former group (no IFN-b, n=5), 4 patients suffered metastasis (3 lymphatic and 1 hematogenous) 10, 13, 39, 84 months after initial treatment. In those, 1 patient with lymphatic metastasis also had early local recurrence 5 months after initial operation. In the latter group (with IFN-b, n=6), neither recurrent nor metastatic disease has found in 6 to 64 months (average 25.8 months) of follow-up. Although statistically not significant (p=0.06), we found the tendency that disease-free survival of the latter group is longer than that of the former group.

Conclusion
Local IFN-b injection may be an effective adjuvant therapy for conjunctival malignant melanoma.

Conjunctival melanocytic lesions: re-appraisal of terminology and proposal for a scoring system for conjunctival melanocytic intraepithelial neoplasia (C-MIN)

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Purpose
To describe the classification, grading and staging of conjunctival melanocytic lesions.

Methods
We have audited our experience with conjunctival melanomas, using a novel mapping system and have found shortcomings in the current 6th Tumour Node Metastasis (TNM) staging system. We have also reviewed our cases of conjunctival melanocytic intra-epithelial neoplasia (C-MIN), conventionally termed conjunctival 'primary acquired melanosis' with and without with atypia. To improve objectivity in the reporting of C-MIN, we propose a scoring system based on: pattern of melanocytic infiltration; density of melanocytes; and degree of cellular atypia.

Results
The term 'conjunctival melanosis' should be used only to describe the slit-lamp appearance of hyperpigmentation. Histologically, this abnormality should be categorized as 'hypermelanosis' or 'melanocytosis'. Hypermelanosis can either be primary or secondary to ocular or systemic disease. Benign melanocytosis comprises conjunctival melanocytic hyperplasia and various forms of naevus. Malignant melanocytosis is essentially melanoma, which is primary ("in situ" or invasive), secondary (i.e. spreading to conjunctiva from adjacent tissues) or rarely metastatic (i.e. from distant sites in the body).

The C-MIN scoring system has been validated with good reproducibility in collaboration with 2 other pathologists. High C-MIN scores essentially represent melanoma in situ, for which there will now be a stage (pTis) in the 7th edition of the TNM staging system for conjunctival melanomas.

Conclusion
We have suggested revisions in the terminology of the classification of conjunctival melanocytic proliferations, and improved the grading and staging of conjunctival melanocytic intra-epithelial neoplasia/melanoma. These developments should be useful in treatment and research.

Thursday

10th September 2009

Uveal tumours

Session 1

Melanocytic tumours

Slow enlargement of choroidal nevi: long-term follow-up of 278 patients

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Purpose
To determine if choroidal nevi enlarge over follow-up of 10 or more years without transformation into melanoma and to identify the factors predictive of nevus enlargement.

Methods
Review of serial fundus photographs of patients with diagnosis of choroidal nevus that had at least 10 years of photographic follow-up. Presumed choroidal nevi that transformed into choroidal melanoma during follow-up were excluded.

Results
Mean basal diameter of nevi was 5mm and mean thickness was 1.5mm. Of 284 choroidal nevi, 31% showed slight enlargement over a median follow-up of 13 years without melanoma transformation. The median increase in diameter was 1mm. Frequency of enlargement was 54% in patients below age 40 and 19% above age 60. On multivariate analysis, young patient age was the only factor predictive of nevus enlargement ($p<0.001$). None of the patients with enlarging nevi received treatment to the nevus and none showed evidence of melanoma metastasis.

Conclusion
About one third of choroidal nevi showed slight enlargement over 10 or more years of follow-up. Frequency of enlargement was inversely related to patient age. We conclude that minimal and slow enlargement of presumed choroidal nevi is common in young patients and, in the absence of other risk factors, does not mandate treatment.

Giant choroidal nevus: clinical features and natural course in 322 cases

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Purpose
Evaluation of clinical features and natural course of giant choroidal nevi (diameter ≥10mm).

Methods
Retrospective clinic-based study of tumor features, tumor outcome and vision outcome.

Results
A medical record review of 4,100 patients diagnosed with choroidal nevus identified 322 (8%) giant choroidal nevi. Median basal diameter was 11mm (range 10 to 24mm). Median thickness was 1.9mm (range 0 to 4.4mm). Retinal findings included drusen (81%), subretinal fluid (8%), orange pigment (1%), retinal pigment epithelial (RPE) detachment (2%), hyperplasia (5%), fibrous metaplasia (15%), atrophy (20%) or trough (2%). Kaplan-Meier estimated transformation into melanoma in 13% at 5 years and 18% at 10 years. Multivariate analyses found close proximity to the foveola ($p=0.017$) and acoustic hollowness ($p=0.052$) were factors predictive of transformation into melanoma. Nevus-related decreased vision was found in 2.2% of eyes at initial visit and 3.7% at final visit (mean 61 months follow-up). Factors associated with nevus-related decreased vision at initial visit included subretinal fluid ($p=0.001$), close proximity to foveola ($p=0.005$), RPE detachment ($p=0.033$), and nevus-related choroidal neovascular membrane ($p=0.044$). Factors predictive of nevus-related decreased vision at final visit included close proximity to the foveola ($p=0.001$) and presence of symptoms at initial visit ($p=0.032$).

Conclusion
Giant choroidal nevus clinically resembles choroidal melanoma but show chronicity such as overlying drusen and RPE alterations. Because 18% show transformation into melanoma by 10 years, long-term monitoring is advised.

Very large choroidal nevi

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Background
Choroidal nevi are usually flat and less than 5mm in diameter. Larger nevi may be difficult to differentiate from small choroidal melanomas. We report 5 patients with a choroidal melanocytic tumor that were large enough to fit the COMS criteria for a large sized melanoma but followed a benign course characteristic of a nevus.

Methods
Documentation of observed natural history of the tumors with clinical, photographic, and ultrasonographic studies.

Results
Patients were followed for a mean of 17.3 years (range 3.6-32.9). Average tumor basal dimensions were 10.1mm x 9.2mm and the height was 2.90 +/-0.20mm. Drusen and RPE changes were present in all tumors, whereas orange pigment was associated with only one tumor. Two of four tumors had associated subretinal fluid. During observation all tumors remained stable in size and none metastasized. All 5 cases were classifiable as large melanomas (COMS) and would have been enucleated if enrolled in the study.

Conclusion
Choroidal nevi may become as large as large choroidal melanomas.

Growth prediction in small choroidal melanocytic lesions: a pilot study on N-isopropyl-p-[^{123}I]-iodoamphetamine

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Background
A positive correlation between increased N-isopropyl-p-[^{123}I]-iodoamphetamine (^{123}I-IMP) accumulation and melanin production is demonstrated. Moreover, choroidal melanomas are notably detected by ^{123}I-IMP single photon emission computed tomography (SPECT) than ^{18}F- fluorodeoxyglucose positron emission tomography. We evaluate whether ^{123}I-IMP accumulation of small choroidal melanocytic lesions is predictive of documented growth.

Methods
Twenty selected patients with small melanocytic lesions less than 12mm in diameter and 3.5mm in height were evaluated. Thirty patients with choroidal melanoma (positive-control group) and 22 patients with other intraocular lesions (negative-control group) were also evaluated. SPECT with ^{123}I-IMP images was obtained 24 hours after intravenous administration of ^{123}I-IMP.

Results
All patients in the positive-control group, one (5%) in the negative-control group, and four (20%) with small melanocytic lesions demonstrated ^{123}I-IMP accumulation. Of four small choroidal melanocytic lesions with ^{123}I-IMP accumulations, three demonstrated documented growth (average follow-up periods, 1.3 years). In contrast, none of the remaining 16 small choroidal melanocytic lesions without ^{123}I-IMP accumulation demonstrated growth.

Conclusion
Preliminary date suggests that ^{123}I-IMP accumulation may reflect intrinsic activity of small choroidal melanocytic lesions.

Fundus autofluorescence imaging of choroidal melanocytic tumors

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Background
To investigate the different pattern of fundus autofluorescence imaging of choroidal melanocytic tumors generated with short-wavelength and near-infrared.

Methods
Thirty-five eyes of 35 consecutive patients affected by choroidal melanocytic tumor performed standard fundus autofluorescence with short-wavelength (SW-AF) and fundus autofluorescence with near-infrared (NIR-AF). Fundus photography, A and B scan ultrasound and OCT were performed. Autofluorescence features of choroidal tumor and overlying retinal pigment epithelium (RPE) were correlated with clinical features.

Results
Twenty-one of 35 choroidal tumors were choroidal melanoma, 14 were choroidal nevi. Flat choroidal nevi had normal SW-AF, while they appeared hyperfluorescent at NIR-AF. Elevated nevi had hyper- and hypofluorescent area at SW-AF and they were hypofluorescent with some small hyperfluorescent spots at NIR-AF in all cases. Choroidal melanoma appeared hypofluorescent with hyperfluorescent spots and halo in all cases in SW-AF and NIR-AF. Drusen and orange pigment appeared both hyperfluorescent in SW-AF, but had a different behaviour in NIR-IR.

Conclusion
Standard autofluorescence (SW-AF) and NIR-AF provide more information about retinal pigment epithelium and retinal changes overlying choroidal melanocytic tumors than about intrinsic autofluorescence of the same lesions.

Panoramic angiography and ICG in uveal melanomas

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Purpose
Study and evaluation of panoramic (150°) ICG and fluorescein angiography in uveal melanomas.

Material and methods
Evaluation of 200 cases of uveal melanomas examined with ICG and fluorescein angiography using the Staurenghi contact lens and HRA2 fundus camera.

Results
The total is composed of 177 cases of nodular and 23 cases of diffuse uveal melanomas. Peritumoral vasodilatation was observed in 70% of small melanomas, 52.5% of medium size melanomas, 30% of large melanomas and 65% of flat uveal melanomas. An intraocular vascular network was observed in 43% of small, 68% medium size, 86% of large and 43% of diffuse uveal melanomas. The presence of peritumoral vasodilatation was inversely proportional to the LTD and high of the tumor. The definition of the tumor borders was the same as the fundus picture in 70% of nodular and 19% of diffuse uveal melanomas. Ischemia of the anterior choroid was observed in 56% of melanomas invading the optic disk and 10% of melanomas without a contact with the optic disk. Peripheral retinal ischemia was present in 19% of the cases. This was related to the extent of the retinal detachment, to the LTD and to the height of the tumor.

Conclusions
Panoramic ICG and fluorescein angiography provides useful and original observations which may be taken in account in the prognosis of conservative irradiation treatment of uveal melanomas.

Correlation of fundus autofluorescence with fluorescein and indocyanine green angiography in choroidal melanocytic lesions

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Purpose
To correlate fundus autofluorescence (FAF) patterns with fluorescein/indocyanine green angiographic (FA/ICGA) features in choroidal melanocytic lesions.

Method
Retrospective chart review of 30 consecutive patients with choroidal nevi and melanoma who underwent FAF photography and FA/ICGA. The FAF pattern was classified as patchy or diffuse. The FA images were evaluated at the arterial, early venous, late venous, midphase, and late phases. The ICGA images were evaluated at the early and midlate phase. The fluorescence within the tumor was classified as hyperfluorescent, pinpoint hyperfluorescent, isofluorescent, or hypofluorescent with respect to the surrounding retina or choroid. Statistical analysis was performed using two sample t test for continuous data. For categorical or ordinal data, Pearson chi-square or Fisher's exact test was used depending on the sample size being studied.

Results
Nineteen of 30 tumors (63.3%) were choroidal melanoma and 11 (36.7%) were choroidal nevus. Thirteen choroidal melanomas had a diffuse FAF pattern. Six choroidal melanomas and 11 choroidal nevi had a patchy FAF pattern. The diffuse FAF pattern was significantly associated with the clinical diagnosis of choroidal melanoma versus choroidal nevus ($P=0.00001$), increased tumor thickness ($P=0.00001$), and increased tumor base diameter ($P=0.001$), partially pigmented or amelanotic versus pigmented lesion color ($P=0.006$), early venous hyperfluorescence on FA ($P=0.015$), and late hyperfluorescence on FA ($P=0.018$).

Conclusion
Diffuse FAF is more often associated with larger choroidal melanomas as well as early venous and late hyperfluorescence on FA angiography.

Intraocular biopsies – results and efficacy of uveal biopsies performed by the Essen biopsy forceps in comparison to other biopsy techniques

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Background
There are several techniques and instruments for performing biopsies of intraocular solid masses. The Essen biopsy forceps was introduced as an alternative approach. The results and efficacy concerning getting a diagnosis should be evaluated and compared to the literature.

Methods
In a retrospective study all intraocular biopsies performed in our oncology service during 2000–2008 were analysed. Age, tumor anamnesis, tumor dimension, biopsy instrument and results were evaluated.

Results
A total of 101 uveal biopsies were performed, 57 by biopsy forceps (group A) and 44 by vitrector (20G/23G/25G) (group B).

Mean age in group A was 72 y. 15 patients had a systemic tumor anamnesis. Tumor height in mean was 4.2mm. There was informative material in 51 patients (89.5%) with a.o. 33 patients uveal melanoma, 6 nevi and 5 metastases. Mean age in group B was 64 years. Fifteen patients had a systemic tumor anamnesis. An informative specimen was found in 33 (75%) patients with a.o. 17 cases of uveal melanoma, 5 metastases and 4 intraocular lymphomas.

Conclusion
Transretinal biopsy of intraocular solid tumors using the vitrector and especially the Essen biopsy forceps is a safe and informative procedure. Further studies are recommended to confirm the results.

Fine needle aspiration biopsy versus punch biopsy for the cytogenetic analysis of uveal tract melanoma

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Background
Alterations in chromosome number including losses or gains of part of the chromosome are strongly associated with long-term patient survival in uveal melanoma. Fluorescence in situ hybridisation (FISH) is a well established and reliable method of detecting these changes. However, concern has arisen over tissue sampling errors that may give inconsistent results when different biopsy techniques are used.

Methods
Tissue for molecular cytogenetic analysis of large uveal tract melanoma was harvested from enucleated eyes. All eyes underwent in vitro transcleral fine needle aspiration biopsy using a 25G needle followed by punch biopsy using an 8mm trephine. All procedures were performed by the same surgeon (VC). Four FISH probes were used to detect numerical changes in chromosomes 3 and 8. FISH studies of both samples were undertaken by two double blinded investigators.

Results
Between May 2008 and April 2009, 18 enucleated eyes underwent in vitro transcleral fine needle aspiration biopsy followed by punch biopsy. Sufficient tissue was available for analysis in 17 of 18 (95%) punch biopsy specimens and 11 of 18 (61%) fine needle aspirates. There was 100% correlation between the cytogenetic reports in eyes that had both a punch biopsy and fine needle aspirate result. 11 of 18 (61%) eyes manifested the poor prognostic feature of monosomy 3.

Conclusion
Fine needle aspiration biopsy and punch biopsy from the same eye produced consistent cytogenetic results. However, even with larger intraocular melanoma, transcleral fine needle aspiration biopsy is limited by difficulties in obtaining sufficient material for FISH analysis.

Observation as a therapeutic option in choroidal melanoma

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Background
The management of suspected small choroidal melanomas is controversial. The purpose of the present study is to assess tumor growth, and survival on choroidal melanoma patients under observation in our Intraocular Tumors Unit.

Methods
Prospective, consecutive and non-interventional case series. Patients diagnosed with choroidal melanoma from 1990 to 2009 and with observation as therapeutic option were included. Criteria for observation were small size without risk factors for growing; medium and large size: no risk factors for growing (but size), advanced age, bad general health, only eye or treatment rejection. Demographic, tumoral and follow-up data were collected in a data base and analyzed.

Results
Eighty-seven out of 346 patients (25.1%) diagnosed with uveal melanoma were enrolled, with mean age of 67.3 years (SD 14.2). The mean follow-up time was 51.5 months (SD 5.4). Regarding the size, 66 (75.8%) tumors were small and 63 (72.4%) were diagnosed in a routine examination. Main reason for observation was tumor small/inactive (59, 67.8%) followed by treatment rejection (22, 25.2%). Mean height was 2.7mm (SD 1.4) and mean base 7.9 (SD 2.3). Along the follow-up, 11 tumors grew (3 small and 8 medium); 10 were treated with brachytherapy and 2 with enucleation. Only 2 patients died during the follow-up by other diseases different of melanoma metastasis.

Conclusion
In our series with more than 4 years of follow up, observation seems to be a safe therapeutic option for selected small choroidal melanomas, allowing the patients to preserve visual function.

Thursday

10th September 2009

Uveal tumours

Session 2

Melanocytic tumours

Laser hyperthermia as a method of choroidal melanoma devitalization before its endoresection

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Background
Choroidal melanoma endoresection as a treatment approach is disputed owing to a high risk of local as well as systemic dissemination. Hence, the development of tumor devitalization methods before its endoresection is an issue of the day.

Aim
To develop a method of choroidal melanoma devitalization before its endoresection.

Materials and methods
To devitalize a tumor, laser hyperthermia using chlorine photosensitizers (669nm; n=12) and contact transretinal thermotherapy using leukosapphire edge light pipe (1,060nm; n=5) were applied. Endoresection was performed on the third day following delimitating and peripheral retina laser coagulation using triple-ported technique (20G and 23G). A set of these methods was considered as enucleation alternative for patients who abandoned liquidation treatment.

Results
In the whole of cases (n=17) the eye was saved as an organ. However, laser hyperthermia using chlorine photosensitizers (n=12) was accompanied by severe exudative retina detachment due to photothrombosis thus preventing endoresection. Contact transretinal thermotherapy using edge light pipe allowed to devitalize tumor mass without significant exudation. This facilitated tumor ablation.

Conclusion
Laser hyperthermia can be applied as a method of choroidal melanoma devitalization before its endoresection. However, this problem requires further investigations.

Transpupillary thermotherapy for residual choroidal melanoma and recurrent tumors: preliminary study

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Background
The aim of our study is evaluate efficiency of transpupillary thermotherapy (TTT) for recurrent choroidal melanoma and residual tumors.

Methods
We analyzed clinical records of 39 patients whom underwent TTT for residual choroidal melanoma and recurrent tumors. All patients were previously treated with brachytherapy.

Results
Follow-up period after brachytherapy before TTT was between 10 months to 10 years. Maximal tumor thickness before TTT was 3.5mm, maximal base diameter was 14.5 mm. TTT was performed using infrared diode laser Nidec DC 3300. Exposure time was 60 seconds. Width of laser beam ranged from 1,400 to 3,000mm. TTT power setting varied from 300 to 900 mV.

We examined in control 35 patients from our group. Maximum follow-up period was 15 months. Twenty five patients showed good response after the one treatment session. There was a flat scar at the place of previous tumor location or gradual decrease of tumor thickness. Doppler ultrasound examination reviled absence of intrinsic vascularity and fluorescein angiography showed absence of leakage. Ten patients had insufficient effect after one treatment session, they underwent 1–2 additional sessions of TTT, nine of them with good outcome. One patient showed tolerance to TTT and was treated by additional brachytherapy.

None of our patients had metastasis at the time of treatment or during follow-up.

Conclusion
Preliminary results of TTT for recurrent choroidal melanoma and residual tumors shows sufficient efficiency in early period after treatment. Long-term follow-up is required to obtain data on local control and late ocular side-effects.

Treatment of choroidal amelanotic melanoma with PDT

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Background
This paper will provide further follow-up on the small consecutive non-comparative case series presented at the ISOO Congress in Siena in June 2007.

Methods
Nine patients with amelanotic choroidal melanomas, one of which had a pigmented portion, underwent PDT using verteporfin as the photosensitising agent. Treatment was repeated at intervals until the melanoma was completely flat or its height had reached a stable end-point. Visual acuity was recorded at each visit and tumour response assessed by clinical examination, colour photography and B-scan ultrasonography.

Results
All nine tumours demonstrated a response to PDT. Four flattened after a single session, four required three treatments and in one it was necessary to apply PDT four times to achieve complete tumour regression. In eight patients there has been no evidence of recurrent growth during total follow-up of between 19 and 76 months, but one case developed a small local recurrence at 21 months. This responded to a further application. The amelanotic portion of the mixed tumour responded to treatment whereas the pigmented part has retained a height of 2mm, which has not altered over the subsequent 20 months. No patient lost vision as a result of treatment and three demonstrated visual improvement.

Conclusion
In this series PDT was highly effective in causing regression of amelanotic choroidal melanomas, without a detrimental effect on vision.

Brachytherapy with ruthenium-106 (Ru-106) plaques for uveal melanoma

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Background
Brachytherapy with radioactive plaques is an established method for treatment of intraocular tumors including uveal melanoma. We will report the results of applying Ru-106 plaque for Iranian patients with uveal melanoma.

Method
This is a retrospective study on 61 patients with uveal melanoma who were treated with Ru-106 plaques from Jan 2003 to Sept 2008. Main outcome measures were local tumor control and patient's survival.

Results
Sixty-one patients were enrolled. Mean follow-up period was 26.98 months (SD 16.8). Mean age of the patients was 52.6 years (SD 14.02). Mean preoperative tumor thickness of 5.40mm (SD 1.89) was decreased to 2.55mm (SD 1.7)($p=0.0001$). Mean radiation dose to tumor apex and sclera was 82.97Gy and 646.39Gy respectively. Tumor control was achieved in 56 patients (91.80%) at last FU. Nine patients needed adjuvant treatment with TTT. Re-application of plaque was necessary for 4 patients because of tumor recurrence. Five patients underwent secondary enucleation. Radiation retinopathy and papillopathy were observed in 41% and 23.1% of eyes respectively. Cataract was developed or increased in 27.9% of the patients. Mean BCVA was 0.66 log MAR preoperatively and 1.25 log MAR at the end of study. All patients, except one, were alive and healthy without apparent systemic metastasis at the end of the follow-up period.

Conclusion
Brachytherapy with Ru-106 plaques is a safe and effective method for treatment of medium sized uveal melanoma. An extended follow-up time is needed to see any further metastasis or recurrent tumor.

Long-term results after ^{106}Ru-brachytherapy for uveal melanoma

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Background
^{106}Ru-brachytherapy is an established treatment modality for uveal melanoma. The aim of this study was to evaluate in a large cohort with long follow-up the local tumour control rate, secondary enucleation rate, rate of metastatic disease and survival outcome after ^{106}Ru-Brachytherapy for uveal melanoma.

Methods
We performed a retrospective study in 948 patients (56.4% females, 43.6% males, mean age: 61.3 years) with choroidal or ciliary body melanomas primarily treated with ^{106}Ruthenium episcleral plaques from October 1992 through December 2005. Clinical and radiotherapy data were extracted from a dedicated database and the survival status was determined through reports from the private ophthalmologist. The Kaplan-Meier method was used for statistical analysis.

Results
The mean follow-up was 5.3 years (0.11–14.3 years). Mean tumor size was 5.1 mm ± 2.1mm (min: 1.0mm; max: 12.3mm) at the time of treatment. 17.7% of eyes showed evidence of ciliary body infiltration and 3.9% had infiltration of the iris. 3.5% of eyes had extraocular growth and half of eyes (50.5%) had retinal detachment. The local tumour control rates were 91.3% and 89.7% at 5 and 10 years, respectively. The eye-preservation was 95.0% and 93.7% at 5 and 10 years, respectively. The reason for secondary enucleation was tumour recurrence in 66.7% and radiation-related complications in 33.3%. At 5 and 10 years, the metastatic rate was 12.5% and 18.5% respectively. The overall and treatment-related survival rates were 90.7% and 95.0% at 5 years, and 83.9% and 91.0% at 10 years, respectively.

Conclusion
^{106}Ru-brachytherapy in the treatment of uveal melanoma is an effective method with a favourable local tumour control and eye preservation rate. Survival and metastatic rates after ^{106}Ru-brachytherapy correspond well with the results of the Collaborative Ocular Melanoma Study.

Local tumour control after ruthenium^{106} brachytherapy for choroidal melanoma

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Background
We evaluated the control rate of choroidal melanoma treated with Ru^{106} plaque brachytherapy to identify the risk factors associated with local recurrence and lack of response.

Methods
A retrospective review of Ru^{106} brachytherapy for patients with choroidal melanoma treated at St Bartholomew's Hospital. Survival analysis evaluated age, sex, location, foveal proximity, tumour base and height, presence of lipofuscin, subretinal fluid, apex dose, radiation rate and type of plaque with time to local recurrence. Logistic regression analysis evaluated the association of the same set of variables with the lack of tumour response.

Results
189 patients were treated from January 2002 to December 2006. The follow-up ranged from 12 to 78 months (median 33 months). None of the patients received adjuvant diode laser. The control rate was 85.7% (14 recurred while 13 did not respond).

Of the patients that had local recurrence, univariate survival analysis demonstrated an association with younger patients, foveal proximity, preoperative subfoveal fluid and tumour base >11mm. However subsequent multivariate analysis revealed the only significant factors for local recurrence were proximity to the fovea ($p=0.04$) and young age ($p=0.04$).

Of the patients that did not respond, logistic regression analysis showed lack of response was associated with a tumour height >5mm, confirmed through multivariate analysis ($p=0.027$).

Conclusion
Tumours that are close to the fovea in young patients are more likely to show local recurrence. Tumour height >5mm was the only prognostic factor that determined lack of response. These results can be used to select which tumours require adjuvant therapy.

Visual acuity after ruthenium^{106} brachytherapy for choroidal melanoma: a 5 year retrospective review

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Background
We retrospectively analyzed the impact of ruthenium^{106} brachytherapy on visual acuity after treatment of choroidal melanoma.

Methods
A 5-year retrospective review of all choroidal melanomas treated with ruthenium^{106} brachytherapy at St Bartholomew's hospital was undertaken. None of the patients received adjuvant diode laser. Logistic regression analysis was used to evaluate the effect of the following variables on visual outcome: radiation rate, apex dose, tumour height and base, tumour location, lipofuscin, subretinal and subfoveal fluid, age, hypertension and diabetes. Visual deterioration of >2 lines on Snellen chart was considered a poor visual outcome.

Results
189 patients underwent treatment with ruthenium^{106} brachytherapy from January 2002 to December 2006. The follow up ranged from 12 to 78 months (median 33 months). Of 189 patients, only 68 (36%) experienced >2 lines deterioration of their visual acuity. Univariate analysis showed an association of poor visual outcome with increasing apex dose ($p<0.01$) and increasing tumour height. Subsequent stepwise multiple variable regression identified that increasing apex dose was the only variable associated with poor visual outcome. The odds of poor visual outcome were 5.3 times greater in patients who received an apex dose of dose of 120Gy compared to an apex dose of 80Gy.

Conclusion
This study reports encouraging rates of visual conservation after ruthenium^{106} brachytherapy, as 64% of patients maintained visual acuity within two lines of their preoperative vision. Radiation rate and tumour location did not have an impact on visual outcome. Visual outcomes were poor for those that required higher doses of radiation.

Ophthalmic brachytherapy using indigenous BARC Ocu-Prosta Iodine-125 seeds for treatment of choroidal melanomas in India

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Background
To report our initial experience of using indigenous iodine-125 seeds for ophthalmic brachytherapy to treat choroidal melanomas.

Methods
We used indigenously fabricated Bhabha Atomic Research Centre (BARC) Ocu-Prosta Iodine-125 seeds developed by Radiopharmaceutical Division, BARC, Mumbai. The treatment planning system used was Plaque Simulator version 5.3.7 by Bebig GmBH. Gold plaques used were slotted and were developed by Eye Physics, LLC. Five eyes of 5 patients were treated. Four were of posterior choroidal and one was of ciliary body melanoma. The average dose calculated was 85 Gy till the apex of the tumor.

Results
Four were medium sized melanomas while one was large sized. The mean height was 7.5mm (range 3.8–13.4mm) and the mean longest basal diameter (LBD) was 10.2mm (range 5.2–13.8mm). Three posterior melanomas were given transpupillary thermotherapy two days before plaque removal while one was given after six months. At mean follow-up of 7.1 months, the mean height was reduced to 4.6–mm while the mean LBD was reduced to 7.5. One case failed to follow-up.

Conclusion
Due to the prohibitive cost of the imported Iodine 125 radioisotope and its short shelf life, it was not feasible to offer brachytherapy to our patients. With the availability of indigenous BARC Ocu-Prosta Iodine-125 seeds locally, cost effective ophthalmic brachytherapy can be offered in India.

High dose rate ^{169}Ytterbium brachytherapy with a collimated applicator for treatment of intraocular melanoma

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Background
A high dose rate (HDR) ^{169}Ytterbium source and associated shielded, collimated applicator are evaluated for afterloading brachytherapy treatment of ocular melanoma. This combination will achieve a dose of 50 Gy to a depth of 5mm within ~20 minutes while limiting dose to normal tissue.

Methods
Dose distributions at various planes within the eye from a plurality of source stopping positions within this collimated applicator were calculated using Monte Carlo methods. The depth-dose profile along the central axis of the eye was also calculated. Monte Carlo results for each stopping position were combined, weighting the dwell time for each position, to achieve an optimized treatment plan. These results were compared to plans using conventional low energy "seeded" plaques and beta plaques.

Results
Higher photon energies from ^{169}Ytterbium results in lower scleral dose than is achieved using lower energy photons and beta sources. Collimation provided by the shielded applicator results in reduction of the lateral extension of the dose distribution, providing greater protection to normal tissue outside the tumor. Individually varying the dwell times at each stopping position resulted in more conformal dose distributions than are achieved with conventional low energy "seeded" plaques.

Conclusion
This superior dose conformality provides collateral improvement in therapeutic response, with potentially better treatment efficacy. Afterloading brachytherapy also reduces radiation dose to the surgeon. The dosimetric performance of the ^{169}Ytterbium source with its shielded, collimated applicator, is suitable for HDR eye brachytherapy. HDR brachytherapy has great promise as a treatment method for ocular melanoma.

Growth in tumour thickness of medium-sized uveal melanoma before ^{125}Iodine brachytherapy as a predictor for post-treatment tumour behaviour

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Purpose
To investigate tumour thickness growth of medium sized uveal melanoma before ^{125}Iodine brachytherapy as a predictor for the clinical outcome post treatment.

Methods
Retrospective case series analysis. Patients with medium-sized uveal melanoma treated by ^{125}Iodine brachytherapy were reviewed for changes in tumour thickness as measured by ultrasonography, during the interval from initial clinical evaluation to one day prior to brachytherapy.

Results
Included in this series were 120 consecutive patients with median follow-up of 29 months. The mean interval from initial evaluation to treatment was 29 days (range 4–81 days). Seventy patients (58%) demonstrated no interval tumour thickness growth and 42% demonstrated growth at a mean rate of 0.03mm/day (range 0.01–0.16mm/day). No significant differences were detected in demographics, tumour dimensions and location between patients with melanoma that demonstrated interval growth versus those who did not. Collar-button configuration has presented in 19% of patients with pre-treatment tumour growth. Following brachytherapy, patients without pre-treatment tumour growth demonstrated no tumour recurrence. Secondary enucleation was required in 3%, and metastases developed in 3%. Patients with pre-treatment growth demonstrated tumour recurrence in 3%. Secondary enucleation was required in 8%, and metastases developed in 9%.

Conclusion
Interval growth of medium sized choroidal melanoma prior to ^{125}Iodine brachytherapy was associated with a greater incidence of tumour recurrence, enucleation and metastases following treatment, and may predict more aggressive tumour behaviour.

Tumour regression after brachytherapy for uveal melanoma: relationship between reduction in tumor height and cross-sectional area

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Background
To describe regression of uveal melanoma, one predictor of metastasis, by its cross-sectional area as compared with height.

Methods
For this retrospective observational study, we identified 168 patients with choroidal melanoma treated with brachytherapy during 2000–2008 and imaged with Innovative Imaging I^3 ultrasound using a standard procedure. Images taken at diagnosis and at 6 months, 1, 2 and 3 years were analysed. Tumour height and area were measured with Olympus DP-Soft, from original digitised images. The software measures the area as traced by hand. These parameters, especially change in tumour cross-sectional area, was analysed according to the status of Bruch's membrane.

Results
The change in height and cross-sectional area of the melanoma after radiotherapy at 6 months, 1, 2 and 3 years were 28 vs. 30%, 33 vs. 37%, 36 vs. 43% and 43 vs. 48% respectively. The corresponding measurements for tumours with an intact Bruch's membrane (75 patients) were 18 vs. 23%, 25 vs. 26%, 32 vs. 32% and 35 vs. 36%, and for tumours with broken Bruch's membrane (61 patients) 36 vs. 38%, 40 vs. 45%, 45 vs. 52% and 54 vs. 56%. When the status of Bruch's membrane was uncertain (22 patients), corresponding reduction was 35 vs.41%, 44 vs. 53%, 49 vs. 52%, and 49 vs. 61.5%.

Conclusion
Reduction in tumour cross-sectional area and height do not differ after 6 months, when uveal melanoma is flat or dome-shaped. Change in area is greater than change in height after 6 months if Bruch's membrane is not intact.

Blood circulation in retina in early terms after brachytherapy of uveal melanomas

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Purpose
To estimate the hemodynamic features in the retinal central artery and vein soon after (1.5 years) brachytherapy in patients with uveal melanoma.

Methods
87 persons (174 eyes) in the age of from 19 to 73 years who had received a local irradiation of an eye concerning the uveal melanoma were examined. With the use of high-frequency duplex scanning Doppler characteristics of blood flow velocity (linear blood flow parameters and indexes of peripheral resistance) in central artery and central vein of the retina were estimated. There were conducted the comparison of average Doppler characteristics of blood flow velocity in tumor's eyes with those in healthy ones which parameters were accepted as normal amounts.

Results
In 1.5 years after brachytherapy in tumor's eyes there were estimated the decreasing of linear blood flow characteristics and the indexes of peripheral resistance in eye vessels. The degree of hemodynamic changes in these vessels were depend on a degree of the tumor's thickness resolution and from it localization in the eye. There were found significant decreased blood flow parameters in eyes with tumors located near to an optic nerve and they were minimal or absent at all when the tumors had pre-equatorial localization.

Conclusion
High-frequency duplex scanning plays the important role in estimation of retinal blood flow changes after brachytherapy of uveal melanomas and in the revealing the first attributes of post-irradiation neuropathy and neuroretinopathy.

Combined pars plana vitrectomy cataract extraction and endolaser ablation for treated uveal melanoma

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Background
To determine the safety of pars plana vitrectomy, membrane peeling, and tumor endolaser ablation at the time of cataract extraction in eyes with brachytherapy treated uveal melanoma.

Methods
A retrospective study of a consecutive series of patients with uveal melanoma treated with I^{125} brachytherapy that underwent combined pars plana vitrectomy, cataract extraction, membrane peeling, intravitreal triamcinolone injection and endolaser ablation of the tumor. Complications, vitreous cytology, and local tumor control were evaluated. Patients with at least 3 months of follow-up after phacovitrectomy were included in the study.

Results
Twenty patients met the study criteria. Patients underwent surgery between September 2007 and September 2008. Surgery was performed a median of 37 months following brachytherapy (range 6–111 months). Pathologic analysis of the vitreous revealed no malignant cells in any case. Clinical and echographic measurements revealed local control of tumors pre- and post-vitrectomy surgery (median follow-up 8 months, range 3–16 months). There were no cases of endophthalmitis. There was one case of hypotony (<5 mmHg), and one new case of cystoid macular edema. Cystoid macular edema was present pre-operatively in 8 cases due to radiation retinopathy. One eye with pre-operative LP visual acuity was enucleated due to a blind and painful eye 7 months after vitreous surgery.

Conclusion
Combined cataract and vitreous surgery addresses modifiable causes of visual loss and fundus obscuration in patients with treated uveal melanomas. Tumors should be clinically and echographically stable prior to vitrectomy. Benefits of this approach include concurrent endolaser ablation of the tumor and evaluation of cytology. The long-term risk of recurrence needs to be determined.

Charged particle therapy of uveal melanoma

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Background
We assessed two important issues in long-term follow-up of uveal melanoma patients treated with charged-particle radiation. First, we evaluated the effect of initial transient enlargement on survival and, second, alteration of beam angles on the incidence of neovascular glaucoma.

Methods
This is a retrospective review of 854 uveal melanoma patients treated with charged particle therapy.

Results
797 patients had stabilization or shrinkage while 57 had initial enlargement followed by shrinkage or stabilization of the tumor. Altered treatment protocols were used to avoid the anterior segment and comparison was made between neovascular glaucoma rates with helium-ion therapy versus a newer approach using protons.

There was a higher percentage of more malignant cells on fine-needle biopsies of patients that had transient enlargement than those whose tumor were stabilized or shrunk ($p<0.01$). Overall, the survival was not different in the groups that had stabilization/shrinkage versus those with initial enlargement followed by stabilization/shrinkage. The incidence of neovascular glaucoma decreased from 30.0% to 6.6% in the different protocols used for charged particle radiation ($p<0.001$). Overall the local control tumor rate was approximately 98.0%.

Conclusion
Charged particle radiation can be used to treat uveal melanoma with excellent local control. Alterations in beam protocols can significantly decrease treatment-related morbidity.

Sixteen years of proton beam radiotherapy for uveal melanomas at Nice Teaching Hospital

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Background
To present the results of uveal melanomas treated at Nice Teaching Hospital since 1991.

Methods
This retrospective study includes 886 consecutive patients referred to our clinic for the treatment of uveal melanomas by proton beam radiotherapy from June 1991 to December 2007. The survival rates were determined by using Kaplan-Meier estimates and the prognostic factors were evaluated using Log-Rank test or Cox model.

Results
Our patients were divided into 399 males and 487 females. The mean age at first consultation was 63.12 years. 137 melanomas were anterior, 318 were at the equator and 431 were posterior to equator. Our patients were staged according to the 6th TNM classification of malignant tumours in T1: 39 (4.4%), T2: 420 (47.40%); T3: 409 (46.16%); T4: 18 (2.03%). The median follow-up was 63.7 months. The Kaplan Meier overall survival rate at five years according to the sixth TNM classification was: T1: 92%, T2: 89%, T3: 67%, T4: 62%; and at ten years, T1: 86%, T2: 78%, T3: 43%, T4: 41%. The metastasis-free survival rate was 88.3% at five years, 76.4% at ten years. The local control rate was 93.9% at 5 years and 92.1% at 10 years. The ocular conservation rate was 91.1% at five years and 87.3% at ten years. The incidence of main ocular complications is discussed.

Conclusion
We report the results of a large series of uveal melanomas with a very long follow-up. Despite the large tumour volume treated, our results were similar to the previously published findings relating to proton beam therapy.

Complications after proton beam therapy for choroidal and ciliary body melanomas with initial height of 7mm or more: a 15 years experience, 1991–2006

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Background
A retrospective analysis of 175 cases among 492 tumors was done. All had an initial thickness of 7mm or more.

Aim
The goal is to analyse the complications, to know which tumors should have an early preventive treatment after radiotherapy.

Methods
Tumors locations were analysed: ciliary body tumors extending or not to the choroid, and choroidal tumors extending to the ciliary body or not, or to the posterior pole. 50 medium tumors and 125 large tumors were included. Mean initial thickness was 8.86 mm, and mean initial LTD 17.50mm. Mean follow-up was 60.39 months.

Initial tumors biometry was described according to fundus locations.

Results
For postequatorial and /or posterior pole locations, neovascular glaucoma (NVG) was found in 36%, whereas maculopathy was not frequent (18%). For equatorial tumors, cataracts and NVG were found in 35 and 30%. For ciliochoroidal locations, high rates for NVG and maculopathy were found (39 and 39%). The highest rates for NVG (45%), cataract (40%), and maculopathy (34%) were ciliochoroidal tumors.

In cases of tumors at less than 3mm from the optic disk, optic neuropathy was seen in only 12%, and if at less than 3mm of the macula, maculopathy in only 17%. Both locations could be associated. Functional results are described.

Metastatic death was seen in 8% of medium tumors and in 10% of large tumors.

Conclusion
NVG was the most frequent complication (37.5%), then cataract (35%), maculopathy is the third one (25%); retinal detachments (8.5%), vasculopathy (8%) and optic neuropathy (7%) being less frequent.

Treatment of post-proton therapy neovascular glaucoma (NVG) with intravitreal anti-VEGF: preliminary results and research project

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Background
Over the last fifteen years, proton therapy as a conservative treatment of uveal melanomas has provided satisfactory local control and survival rate in our unit. However, regarding melanomas with a thickness greater than 8mm, we have obtained a troublesome rate of neovascular glaucoma (33.8%). Overall, complications required enucleation in 25% of treated bulky melanomas versus 5.8% for other melanomas.

Methods
Recent studies have shown an increased rate of VEGF-A in eyes with uveal melanomas. Moreover, this increase was correlated with prior radiotherapy. Since October 2008, a last chance anti-VEGF therapy has been administered in eyes presenting with not controlled NVG despite maximal treatment. So far, we have performed one to two intravitreal injections in 6 patients.

Results
In all cases, rubeosis disappeared; intraocular pressure levels returned to normal with or without anti-glaucoma drops. No patients suffered from pain and exudative retinal detachment decreased in a few cases. However, the number of cases has so far been too small to perform statistical analyses. These preliminary results seem interesting, although they are collected through a non-randomized study with no standardized protocol.

Conclusion
Regarding the future, we would like to undertake a research project with the CNRS (National Organization for Scientific Research). It aims at identifying biological markers enhancing risk of NVG in uveal melanomas, and testing a treatment for post protontherapy NVG using intravitreal anti-VEGF.

Visual outcomes after proton beam irradiation for choroidal melanomas involving the macula

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Purpose
To investigate rates of vision loss in patients with choroidal melanomas near or involving the fovea after treatment with proton beam irradiation (PBI).

Methods
Visual outcomes after proton beam irradiation were evaluated in 325 patients with choroidal melanomas located ≤1DD from the fovea and >1DD from the optic nerve, resulting in full-dose exposure to the fovea. Median follow-up among patients without vision loss was 33.5 months.

Results
Cumulative rates of vision loss to worse than 20/200 for the overall group were 18.8% at 1 year, 46.2% at 3 years, and 65.5% at 5 years after PBI. The median time to vision loss was 26.3 months. Eyes with tumors >5 mm in height had a 2.5-fold increased risk of vision loss compared to those with tumors ≤5 mm ($p<.001$). The risk of vision loss also correlated with baseline visual acuity. At 5 years after PBI, 48.5% of eyes with baseline acuity of 20/40 or better had vision loss to <20/200 whereas 72.5% of eyes with baseline acuity of 20/50-20/100 lost vision to <20/200 ($p=.001$).

Conclusion
While treatment of macular tumors with proton beam irradiation results in severe vision loss in the majority of patients after 5 years, a significant proportion retain useful vision. Smaller tumor height and better baseline visual acuity are favorable prognostic factors for vision retention.

Eye retention and survival rate following proton beam therapy for uveal melanoma in Scotland

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Background
Uveal melanoma, while rare, is the most common primary adult ocular malignancy. The Tennent Institute is the tertiary referral unit for uveal melanoma in Scotland. Treatment aims to control local disease and prevent systemic spread. A secondary aim is eye retention. Proton beam therapy (PBT), a recognised treatment, avoids primary enucleation.

Method
The aim was to determine patient survival and eye retention rate for all uveal melanomas treated with PBT from the Scottish Ophthalmic Oncology Service 01/01/95– 31/03/08. Patients were identified from the oncology database. Demographic, clinical, treatment and outcome data was identified from database information and retrospective case-note review.

Results
150 patients underwent PBT for uveal melanoma, 25.6% of all diagnosed. This consisted of 139 choroidal, 7 ciliary body and 4 iris melanomas. The mean maximum height was 8.1mm (SD 2.8), the mean maximum diameter was 17.0mm (SD 4.74).

Thirty-four (22.7%) required subsequent enucleation. The mean time from PBT to enucleation was 23.2mths (range 2.1–68.6mths). Suspected primary treatment failure or recurrence was the reason for enucleation in 48%, neovascular glaucoma was the indication in 42%. Five-year eye retention rate for all uveal melanomas treated with PBT was 71.4%.

Eleven (7.3%) died from metastatic disease, seven had previously undergone enucleation. Time from diagnosis to death from metastases ranged from 7.9–70.4 months. Five-year metastases free survival was 90.6%.

Conclusion
PBT is used successfully to treat appropriately selected uveal melanomas in Scotland. Eye retention rate and patient survival in these patients is comparable to data published from other centres for similar sized lesions.

Long-term survival in patients with uveal melanoma treated with proton therapy

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Background
We evaluated long-term survival in a large series of patients with uveal melanoma up to 25 years after completing proton therapy.

Methods
Patients (N=2266) treated between 1975 and 1998 were followed through December 2006 (median follow-up time among surviving patients: 16.5 years; range: 8.0–31.5). Vital status and cause of death were ascertained by active follow-up or searches of the Social Security Death Index and National Death Index. Cumulative rates of melanoma-related mortality were calculated using the Kaplan-Meier method. Cox regression analysis was completed to assess prognostic factors.

Results
Twelve patients were alive with metastasis and 530 had died of melanoma at the end of the observation period. Annual rates of melanoma-related deaths peaked at 3% to 4% between 3 and 6 years after treatment. These rates diminished over the next decade, dropping below 1% 14 years after treatment. Cumulative 15 and 20-year mortality rates were 26% and 27% respectively. Multivariate Cox regression analysis confirmed that largest tumor diameter is the most important clinical predictor of melanoma mortality, with a 20% increase in risk associated with each 1mm increase in size (RR: 1.2; 95% CI: 1.19–1.26, $p<.001$).

Conclusion
Patients continue to be at risk of death due to melanoma more than 20 years after treatment, with annual rates of less than 1% observed by 14 years after treatment.

Treatment of juxtapapillary melanoma: proton beam versus notched ruthenium plaque brachytherapy

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Background
The debate as to the ideal treatment for juxtapapillary melanoma is ongoing. It is generally accepted that there is little difference in survival between the three main choices of treatment – enucleation, charged particle radiotherapy, or plaque brachytherapy. Elucidating the treatment that minimises local recurrence, and provides the lowest incidence of radiation side effects is of paramount importance.

Methods
A retrospective analysis of all juxtapapillary choroidal melanomas treated between 1985 and 2000 by either proton beam or notched ruthenium plaque brachytherapy was undertaken. Patients who received plaque with adjuvant treatment were excluded from the initial analysis. All patients were followed up in the London Ocular Oncology service for local recurrence and the incidence of radiation side effects. Data was analysed using GraphPad Prism 4.02 (GraphPad Software Inc).

Results
Sixty-four patients (42 proton beam, 22 plaque brachytherapy) were identified as having juxtapapillary melanomas suitable for treatment by either modality. All patients had a minimum follow-up period of three years. Pre-operatively, there were no significant differences between groups in terms of vision, tumour location, or tumour dimensions. Three years post operatively, extra temporal juxtapapillary tumours treated with notched ruthenium plaques had significantly better vision than those treated with proton ($p=0.018$ unpaired t-test). There was no significant difference in terms of radiation side effects between the two groups. There was no significant difference in local tumour recurrence between the two treatments.

Conclusion
Extra-temporal juxtapapillary choroidal melanomas treated with notched ruthenium plaque brachytherapy have significantly better preserved visual acuity than those treated with proton beam at three years. There is no other significant difference in local tumour recurrence or other radiation side effect when treating juxtapapillary melanoma by these modalities.

Proton beam irradiation in choroidal melanoma with sizeable extraocular extension

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Objective
We report on the successful management of choroidal melanoma with sizeable extraocular extension by means of proton beam irradiation.

Method
Retrospective, interventional case series of three patients. Most important to calculate the tumor volume including the extrascleral extension is the segmentation and delineation by means of MRT to allow a precise calculation of the radiation dose.

Results
Follow-up in the three patients was 10, 12 and 24 months. Treatment parameters were 4 x 15 CGE after tantalum clip placement. The mean thickness of the intra- and extraocular tumor component was 4.3mm (3–6.4mm) and 5.4mm (2.5–10.2mm) and showed a 35% and 40% regression, respectively. Visual acuity remained unchanged in two patients and dropped 5 lines in one patient due to radiation maculopathy. No patient developed metastatic disease.

Conclusion
Extraocular extension in choroidal melanoma can be successfully managed by treatment planning after MRT evaluation and proton beam therapy with preservation of function.

Recurrence of the uveal melanoma in the orbit: abilities of proton beam irradiation

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Background
Uveal melanoma is a dangerous condition and may relapse in the orbit after enucleation of the eye. Such condition bears considerable metastatic potential and orbital exenteration, which significantly deteriorates quality of life, is a conventional treatment in those cases.

Methods
We investigated the group of 36 patients with recurrence of uveal melanoma in the orbit after enucleation. Median age of the patients was 50.3 years with range 14–73 years. All of them received average dose of 70.5 Gy in 4–6 sessions of proton beam irradiation through single frontal entry.

Results
Complete regression of the tumor was observed in 16 patients (44%) through 14 months after irradiation as average. In 4 cases tumors diminished partially and not revealed any signs of growth at the time of last examination. In 9 cases treatment was unsuccessful and orbital tumors progressed. Metastases in the liver, lungs, brain, bones, lymph nodes and subcutaneous tissue developed in 14 (39%) of the patients with median time of 19.5 months after proton irradiation.

Conclusion
Proton beam irradiation is an effective method to treat the recurrence of uveal melanoma in the orbit after enucleation. Proton therapy allows achieve complete or partial tumor regression in 55% of cases and may be used as alternative to orbital exenteration.

Thursday

10th September 2009

Uveal tumours

Session 3

Melanocytic tumours

Macular morphological changes following stereotactic radiosurgery for uveal melanoma

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Purpose
Stereotactic radiosurgery is one of the methods to treat uveal melanoma. The time of onset of complications after therapy such as macular edema following irradiation evaluates this study by using ultrasound B-scan and OCT (optical coherence tomography) findings.

Methods
The case series included 32 patients treated for uveal melanoma by stereotactic radiosurgery (C-LINAC). The therapeutic dose was 35 Gy (TDmax 42Gy). Patients were evaluated in 6-month interval after stereotaxy by ophthalmoscopy, B-scan ultrasound, MRI (magnetic resonance), fundus photodocumentation and OCT.

Results
Patients were treated from 2001 to 2007; median follow-up was 24 months. The mean time to onset of macular edema by OCT was 12 months.

The development by OCT evident macular edema was significantly associated with maximum tumor thickness, largest tumor base, distance of the tumor margin (irradiation border of the stereotactic planning scheme) from the macula.

In the 12 month interval after stereotaxy the radiation therapeutic dose was not significantly associated with the development of macular edema.

Conclusion
OCT and ultrasound B-scan is the most important way in early detection of radiation-induced macular changes. OCT is important to detect radiation-induced macular edema before clinical signs of radiation maculopathy develop. The development of macular edema is significantly associated with the volume of the irradiated tumor and the distance of the margin of the base of the irradiated tumor.

Comparison between ^{125}Iodine brachytherapy and stereotactic radiotherapy in the management of juxtapapillary choroidal melanoma

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Purpose
To compare between ^{125}Iodine brachytherapy (IBT) and stereotactic radiotherapy (SRT) in the management of medium-sized juxtapapillary melanoma.

Methods
A comparative interventional retrospective study. Patients with medium-sized juxtapapillary choroidal melanoma treated by radiotherapy were divided into 2 cohorts, those who were treated by IBT and those with SRT. Demographics, tumour characteristics, and radiotherapy-related data including radiation doses delivered to corresponding ocular points and radiation consequences were reviewed for each group.

Results
Median follow-up was 48 months in both groups. The IBT cohort included 30 patients with tumour edge located 0.75–2.5mm from the optic disc. Median tumour thickness was 4.3mm and median longest tumour diameter was 9.9mm. SRT cohort included 64 patients with tumour edge located 0–2mm from the optic disc. Median tumour thickness was 4.2mm and longest tumour diameter was 9.8mm. In the IBT treated patients tumour control rate was 90%, eye preservation was 90%, and metastases developed in 7% of patients, compared to 90%, 84%, and 15% respectively in SRT treated patients. Radiotherapy complications in IBT treated patients included cataract in 53%, neovascular glaucoma 10%, retinopathy 53%, and papillopathy 33%, compared to 60%, 42%, 81%, and 64% respectively in SRT treated patients.

Conclusion
IBT and SRT provide comparable tumour control and eye preservation rates in the management of medium-sized choroidal melanoma close to the optic nerve. However, SRT is associated with significantly higher long-term radiation-induced ocular morbidity.

Irreversible electroporation for uveal melanoma: a possible new treatment modality

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Background
Irreversible electroporation (IRE) is a novel tool for treating solid tumors by applying high electrical field pulses on the target tissue. The goal of this pilot study was to evaluate the effect of high electrical field on normal rat eye pathology and to evaluate the optimal electrode configuration and pulse parameters that will induce maximal tumor eradication using IRE.

Methods
Rats were anesthetized and stainless steel electrodes were placed on the limbus or equator position. Eyes were treated using 10–100 electrical pulses of 1500 volt/cm with pulse duration of 100 microseconds. The animals were euthanized 24 hours after the procedure and eyes were fixed in formaldehyde, processed, cut and stained for light microscopy. Pathological results were compared to simulation model.

Results
H&E staining of rats' eyes 24 hours after pulse treatment to the equatorial or limbic region revealed localized retinal and uveal destruction with minimal or no damage to the sclera. The damage was localized to a radius of about 2mm around the electrodes' position. A significant inflammatory response in the eye was demonstrated. Simulation data demonstrated that an internal electrode can achieve a higher electrical field; however, target electrical field can still be achieved using an external electrode. According to the simulation, tumor electrical conductance has a major effect on treatment efficiency.

Conclusions
Electrical field applied by external electrodes can produce a relatively localized effect on eye tissue. Human as well as animal studies are needed in order to explore the potential of IRE in treating uveal melanoma.

Proliferative radiation retinopathy following plaque radiotherapy for uveal melanoma

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Purpose
To determine risk factors, incidence, management and outcome of proliferative radiation retinopathy (PRR) after plaque radiotherapy for uveal melanoma.

Design
Case-control study.

Methods
Retrospective review of medical records. Main outcome measure: PRR after plaque radiotherapy for uveal melanoma.

Results
Of 3,841 eyes treated with plaque radiotherapy for uveal melanoma, PRR developed in 5.8% at 5 years and 7% at 10 and 15 years using Kaplan-Meier analysis. The mean time to onset of PRR was 32 months (median 30 months, range 4–88 months). On univariate analysis, baseline factors predictive of PRR ($p<0.05$) included young age, diabetes, Hispanic race, shorter tumor distance to the optic disc and the foveola, Bruch's membrane rupture, choroidal tumor location, subretinal fluid, higher radiation dose to the optic nerve and the foveola, additional transpupillary thermotherapy, and notched plaque. In the multivariate model, young age (odds ratio [OR], 1.45; 95% confidence interval [CI], 1.28–1.63, per decade decrease) and diabetes mellitus (OR, 2.23; 95% CI, 1.15–4.35) were related to the occurrence of PRR. The most common forms of management included panretinal photocoagulation (70%), vitrectomy (21%) and observation (17%). Resolution of the neovascularization was obtained in 63% of eyes after treatment.

Conclusion
PRR developed in 7% of eyes by 10 years following plaque radiotherapy for uveal melanoma. The main factors for development of PRR included young age and pre-existent diabetes mellitus.

Treatment of radiation oculopathy due to I-125 brachytherapy of uveal melanoma with intravitreal bevacizumab, transpupillary thermotherapy, and surgery

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Background
Radiation oculopathy is a cause of vision loss in patients receiving I-125 brachytherapy. The purpose of this case series is to determine whether intravitreal bevacizumab (IVB) with or without adjunctive transpupillary thermotherapy (TTT) or surgery mitigates this vision loss.

Methods
A consecutive series of 20 patients presenting with progressive vision loss due to radiation oculopathy were treated with IVB injection(s). The patients were sorted into groups based on pathophysiology; maculopathy, vitreous hemorrhage, neovascular glaucoma (NVG), or papillopathy. Visual acuity was measured with Snellen method, and macular edema was measured with spectral OCT.

Results
The mean follow-up was 12 months (range 5 to 24 months), and the mean number of injections was 3 (range 1 to 8). Macular edema (ME) improved or stabilized in 7/9 patients. Vitreous hemorrhages benefited from vitrectomy in 4/5 patients. TTT was applied as an adjunctive therapy and was correlated with vision improvement in 3/4 patients. NVG was responsive to the therapy with regression of NVI and normalization of IOP in 2/2 patients. No adverse effects on tumor characteristics were detected.

Conclusion
This small study suggests IVB is a safe and useful adjunctive therapy for radiation oculopathy. Surgery and/or TTT therapy are useful adjunctive treatments. The limitations of this study are its small size, short follow-up period, and the lack of a randomized control population.

Sector laser photocoagulation for prevention of macular edema following plaque radiotherapy for uveal melanoma

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Objective
To investigate the potential benefit of sector laser photocoagulation for prevention of macular edema following plaque radiotherapy for uveal melanoma.

Methods
Comparative non-randomized interventional study that included 61 patients with uveal melanoma who underwent plaque radiotherapy. The treatment group included 31 patients who received application of sector laser photocoagulation around the tumor in one session after plaque. The historical comparison group included 30 patients treated with plaque radiotherapy without laser. Patients were evaluated at 4, 8, 12 and 18 months following plaque application with clinical examination, fundus photography and optical coherence tomography (OCT). Main Outcome Measure: OCT-evident macular edema.

Results
At 18 months of follow-up, patients in the laser group had a lower rate of OCT-evident macular edema than controls (36% vs 68%). No major side effects were registered.

Conclusion
Sector laser was a useful and safe intervention for the prevention of macular edema following plaque radiotherapy for uveal melanoma in this series.

A pilot study comparing the efficacy of intravitreal bevacizumab versus intravitreal triamcinolone in the treatment of macular oedema following plaque radiotherapy for uveal melanoma

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Purpose
To compare the short-term efficacy of intravitreal bevacizumab versus intravitreal triamcinolone in the treatment of macular oedema following plaque radiotherapy for uveal melanoma.

Methods
A comparative interventional series of 25 cases.

Results
At 3-months follow-up mean reduction in central foveal thickness was 182μm in the triamcinolone group compared to 49μm in the bevacizumab group. Vision gain of one line or more was achieved in 61% of the triamcinolone group compared to 14% of the bevacizumab group.

Conclusion
Intravitreal triamcinolone may be more effective than intravitreal bevacizumab in the treatment of macular oedema following plaque radiotherapy of uveal melanoma. A larger controlled study is warranted.

Trans-scleral resection of choroidal melanoma

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Background
To report the results of trans-scleral resection of choroidal melanomas performed between 1999 and 2008.

Methods
Trans-scleral local resection was performed with a lamellar scleral flap, using systemic hypotensive anaesthesia to reduce haemorrhage. Adjunctive brachytherapy was administered either at the same operation or during the next few weeks. Follow-up studies were restricted to patients residing in mainland Britain.

Results
The 85 patients (31 female, 54 male) had a median age of 51 years. The tumours had a mean basal diameter of 14.4mm and a mean thickness of 8.0mm with 87% extending posterior to equator and 37% involving ciliary body. Epithelioid cells, closed loops, a high mitotic rate and monosomy 3 were present in 73%, 41%, 32% and 19% of tested tumours respectively. Four procedures were abandoned. With adjunctive brachytherapy, the 8-year actuarial rate of local tumour control was 85%. Retinal detachment occurred in 14% of eyes. The actuarial 8-year rate of ocular conservation was 77%. The last known visual acuity was 6/12 or better in 37%, 6/18 to 6/60 in 19%, 3/60 to counting fingers in 21%, hand movements to light perception in 4% and enucleated in 20%. The actuarial 8-year metastatic mortality was 5% in patients with an apparent disomy 3 melanoma and 65% in patients with monosomy 3.

Conclusion
Trans-scleral local resection can conserve eyes with a large choroidal melanoma when other methods are considered unsuitable.

Long-term results after endoresection with pre-treatment by single-dose stereotactic convergence irradiation and adjuvant brachytherapy in large uveal melanomas

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Background
The aim of this retrospective, non-comparative, consecutive case study is to evaluate the long-term results after single-dose stereotactic convergence irradiation, endoresection and brachytherapy in large uveal melanomas, particularly regarding functional outcome, secondary complications, additional surgery and tumour control.

Methods
This retrospective case study included 113 patients treated in the period from March 1999 to July 2008. All patients underwent single-dose stereotactic radiosurgery followed by endoresection and adjuvant brachytherapy with ruthenium^{106}. The average tumour height was 9.5mm and the median follow up 23.8 months.

Results
The median postoperative visual acuity was 0.05 with 19 patients (16.8%) retaining a visual acuity of 0.3 or better. Complications included serious haemorrhages in 12 patients (11.7%) directly following surgery, a retinal detachment in 17 patients (15%), a secondary glaucoma in 11 (9.7%) patients and in 14 patients (12.4%) a radiogenic retinopathy. One patient experienced a serious scleromalacia. Additional major surgery was required in 26 patients (23%). In total 15 eyes (13.3%) were enucleated due to serious complications or insufficient tumour control. Tumour recurrences were observed in six cases leading to an additional treatment with ruthenium in 2 patients (1.77%) or a transpupillary thermotherapy in the remaining four (3.54%).

Conclusion
For large uveal melanomas, endoresection and brachytherapy following single-dose stereotactic convergence irradiation is often the only eye and vision saving treatment option. A fair residual visual acuity was maintained in several patients.

Vitreoretinal surgery and endoresection in posterior choroidal melanoma after radiotherapy

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Background
Eyes with uveal melanoma sometimes need surgical intervention cause of radiation induced retinal complications. We report visual outcome, complications and enucleation rates.

Methods
Thirteen patients (10 men and 3 women) with posterior uveal melanoma were treated (twelve with Leksell-Gamma-Knife, one with ruthenium-106 brachytherapy). Largest basal diameter ±SD was median 11.7 ±4.1mm (range 8.3–20mm) and median tumor height was 8.6 ±2.9mm (range 4.3–16.5mm). Interval between radiation and endoresection was 8 months ±8.9 in median (range 0.5–25 months). Except one patient (vitreous hemorrhage) all patients developed a retinal detachment with more than 2 quadrants involved. Vitrectomy was performed, followed by retinotomy, melanoma removal with a vitrectomy probe, retinal reattachment with perfluocarbon liquid and silicone oil.

Results
Mean patient age was 64 years ±14.9 (range 42–88 years). Preoperative visual acuity ranged from hand motion to 20/20 and postoperative visual acuity from no light perception to 20/200. One blind painful eye was enucleated because of corneal ulceration. No tumor recurrences were seen. Six additional operations after primary intravitreal surgery had to be performed (four vitrectomies, one enucleation and one lavage of the anterior chamber). Two patients developed distant metastases (15%).

Conclusion
These data show that combined vitreoretinal surgery and endoresection after radiation are an acceptable management option for preservation of the globe and the residual visual function in uveal melanomas with retinal detachment or vitreous bleeding.

Cataract extraction and implantation of an artificial iris with IOL after block excision of iridociliary tumours

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Background
Coloboma of the iris and complicated cataract decrease the functional results after block excision of the iridociliary tumors. To increase visual acuity, cataract extraction with and without implanted artificial iris was performed.

Materials and methods
125 block excisions were performed. 41 patients (32.8%) had senile or complicated cataract. In 23 cases tumour was removed simultaneously with cataract extraction with IOL. In 18 cases cataract extraction with IOL was delayed and in 4 of those cases the reconstruction of the anterior chamber was performed with the help of artificial iris with IOL (elastic material based on metacrylic oligomer). Visual acuity prior to operation on average amounted to 0.06. Follow-up period comprised on average 1.8 years.

Results
Visual acuity has increased to 0.5 after surgery. In the early post-op period, the following were observed: swelling of the cornea and transitory hypertension. Long after the operation, in one case there was epithelial/endothelial dystrophy of the cornea. All patients considered the cosmetic effect favorable.

Conclusion
The given clinical cases show that cataract extraction and implantation of an artificial iris with IOL makes it possible to increase visual acuity and to obtain a favorable cosmetic effect. However, contraindications to the implantation of artificial iris with IOL are malignant tumours and dystrophic and ischemic changes in the anterior segment, which may lead to epithelial/endothelial dystrophy of the cornea.

Thursday

10th September 2009

Uveal tumours

Session 4

Melanocytic tumours

Metastasis of iris, ciliary body, and choroidal melanoma in 8,033 patients

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Purpose
To evaluate uveal melanoma metastasis based on tumor location and size.

Method
Retrospective review of 8,033 cases.

Results
At 3, 5, and 10 years, melanoma metastasis was detected in <1%, 4%, and 7% of iris melanoma, 12%, 19%, and 33% of ciliary body melanoma, and 8%, 15%, and 25% of choroidal melanoma. Of all 8033 melanomas classified as small (<3mm thickness), medium (3.1–8mm), and large (>8mm), metastasis was found in 12%, 26%, and 49% at 10 years and 20%, 37%, and 67% at 20 years, respectively. More specifically, metastasis per millimeter increment at 10 years was 6% (0–1.0mm thickness), 12% (1.1–2.0mm), 12% (2.1–3.0mm), 16% (3.1–4.0mm), 27% (4.1–5.0mm), 28% (5.1–6.0mm), 29% (6.1–7.0mm), 41% (7.1–8.0mm), 50% (8.1–9.0mm), 44% (9.1–10.0mm), and 51% (>10.0mm).

Conclusion
Increasing size of uveal melanoma is associated with increasing risk for metastasis.

CNS metastasis from malignant uveal melanoma: a clinical and histopathological characterisation

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Purpose
To characterise uveal melanoma that has metastasised to the central nervous system (CNS).

Methods
Review of 2,365 patients constituting all patients diagnosed as having primary uveal melanoma in Denmark during the period 1943–1997. All patients with malignant uveal melanoma and metastasis to the CNS were identified. For each patient, clinical and histopathological data were gathered.

Results
Sixteen patients with CNS metastasis were identified. The median age was 58 years. The majority of CNS metastases were located in the frontal and parietal lobes. Eleven patients had widespread metastases. Five patients had exclusively metastasis to the CNS. The average time from diagnosis of primary tumour to symptoms of CNS metastasis was 91 months. The average time from the initial CNS symptoms to death was 20 months. All tumours were composed of either mixed or spindle cells. The average largest basal diameter of the primary tumours was 12mm. One tumour was a ring melanoma. The majority of tumours had a ruptured Bruch's membrane. Retinal invasion was observed in 36% of tumours. No specimen had optic nerve invasion. Scleral invasion was pronounced in 36% of cases, and extrascleral extension was observed in two cases (14%). The amount of tumour infiltrating lymphocytes was pronounced in three cases (23%).

Conclusion
The proportion of uveal melanoma patients having CNS metastasis was 0.7%. Eleven patients had multiple organ metastases, and the average time from the initial CNS symptoms to death was 8 months. Five patients had metastasis to the CNS solely, and the average time from the initial CNS symptoms to death was 57 months.

Whole body PET/CT: initial screening for metastatic choroidal melanoma

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Background
To report our experience with whole body PET/CT screening for metastatic choroidal melanoma.

Methods
251 consecutive patients were diagnosed with choroidal melanoma and underwent screening for metastatic disease with PET/CT scan, liver function tests and physical examination. PET/CT results suspicious for metastatic melanoma prompted further biopsies, imaging and/or clinical evaluations for confirmation.

Results
52 (21%) of patients screened for metastatic melanoma had suspicious non-ocular PET/CT results. Seven of 251 (2.8%) of patients were found to have metastatic choroidal melanoma. Eight (3.2%) were diagnosed with synchronous second cancers and 37 (14.7%) had benign lesions. The most common metastatic sites were liver (n=7, 100%), and osseous (n=2, 28.6%), lung, brain, spleen, lymph nodes and subcutaneous tissue (each n=1, 14.3%). Using AJCC-UICC tumour staging criteria, these seven melanomas were staged as T2N0M1 (n=1), T3N0M1 (n=1), T4N1M1 (n=1), and T4N0M1 (n=4); by COMS criteria, there was 1 medium and 6 large melanomas representing 1.6% of all T2 melanomas, 2.4% of T3 and 13.8% of T4 or 0.6% of medium and 12.5% of large melanomas. Six patients with metastatic uveal melanoma were confirmed by biopsy and one died soon after diagnosis.

Conclusion
PET/CT-imaging is commonly and widely used to stage metastatic malignant melanoma. In this series current FDG-18 PET/CT did little better than radiographic abdominal imaging (CT/MRI) for initial metastatic choroidal melanoma screening. However, the high yield (12.5–13.8%) for patients with large COMS or T4 tumours could justify its use in this subgroup. Moreover, liver PET/CT results had a 100% positive predictive value in our study population, regardless of melanoma size.

MRI versus FDG-PET scan in patients with liver metastases from uveal melanoma: a prospective study with intraoperative confirmation

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Background
Resection of liver metastases is proposed to treat liver metastases of uveal melanoma (UM); microscopically complete (R0) resection of metastases improves median survival from 22 versus 9 months if incomplete surgery. The aim of this study was to compare the sensitivity of dynamic-enhanced MRI with FDG-PET in the pre-operative diagnosis of liver metastases UM.

Methods
15 consecutive patients (mean age 56 years (range 38–71)) underwent FDG-PET scan and liver MRI. All patients had suspected liver metastases following screening by hepatic US and/or CT scan. Extrahepatic metastatic disease was excluded by whole body CT scan and bone scintigraphy. MRI and FDG-PET were performed a mean of 19 days before surgery. Imaging findings were compared with surgical and histological findings on a lesional basis.

Results
28 lesions were resected with 27 metastases being histologically proven. There were 9 (33.3%) lesions <5mm, 7 (26%) 5–10mm and 11 (40.7%) >10mm. Sensitivity and positive predictive value were 66.7% and 94.7% for MRI compared to 40.7% and 100% on FDG-PET. The difference between the two methods was statistically significant ($p=0.01$; Mac Nemar test). In the remaining 3 patients, diffuse miliary disease (>10 capsular lesions) was discovered intra-operatively, 2 of which had been suspected on pre-operative MRI.

Conclusion
In this study, MRI is superior to FDG-PET for the detection of hepatic metastasis of UM. Whilst in some cases miliary disease was suggested by MRI, preoperative confirmation remains imperfect so, when miliary disease is suspected, laparoscopy exploration prior to formal surgery is recommended.

Pilot study of adjuvant immuno-chemotherapy for high risk uveal melanoma: a single-center experience with thirty-one patients

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Background
Uveal melanoma is the most common primary intraocular malignant tumor and despite successful local tumor control, overall mortality rate remains high.

Methods
Between March 2001 and December 2007, thirty-one high-risk patients with uveal melanoma (10 with medium and 21 high tumor size) were enrolled into a pilot trial of adjuvant immuno-chemotherapy. We measured tyrosinase mRNA levels by real time quantitative RT-PCR in blood of all patients during a period of 5 years. Results were correlated with clinical data and with the number of circulating tumor cells evaluated by ISET. The therapeutic regimen consisted of fotemustine 100mg/m^2 endovenously on days 1–8 of the first month and after one administration every four weeks for six months. Interleukin-2 was given subcutaneously at the dose of 4.5 million IU daily for 5 days a week for 2 consecutive weeks every month for 6 months as immunotherapy.

Results
All patients received a median of 5.6 cycles (range 4–6) and were evaluated for toxicity and response. After a follow-up period of 5 years, 25 patients (83%) were still alive without recurrences, 5 died for liver metastases (17%). A significant correlation was found between mRNA tyrosinase levels and tumor size ($p<0.01$), disease free and overall survival ($p<0.05$). All patients who developed metastasis showed an increase in tyrosinase mRNA levels and positivity to ISET.

Conclusion
Our data indicate that fotemustine and interleukine-2 as adjuvant treatment of high-risk uveal melanoma patients is well tolerated and is associated with a very low rate of metastatic recurrences.

The role of nm23 and CD117 in the regulation of uveal melanoma growth

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Background
nm23 suppresses tumor metastasis as well as participates in cell differentiation and proliferation. Another regulator protein, CD117, produces metastatic signal. From this viewpoint, uveal melanoma (UM) is the least investigated tumor.

Aim
To discover the role of biological markers nm23 and CD117 in UM pathogenesis and disease prediction.

Materials and methods
53 preserved paraffin UM blocks (39 primary UM and 14 UM metastases) were investigated using immunohistochemical markers nm23 and CD117 (DAKO, Denmark). Expression type and rate were analyzed. In patients with diametrically opposite nm23 and CD117 expression values, Kaplan-Meier survival was calculated.

Results
In 34 of 53 UM (68%), nm23 expression was detected. Protein synthesis occurred in UM cell nuclei. The expression increased with patients' age ((k=0.30, p=0.034) and atypia augmentation (k=0.34, p<0.032). Non-pigmented UM were nm23-negative. No significant differences in 3-year and 5-year Kaplan-Meier survival between $nm23^+$ and $nm23^-$ UM patients were identified. In 6 UM (15%) CD117 was absent. In 11 UM (28%) the expression was poor, in 10 cases (26%) it was moderate. CD117 over-expression was observed in 12 primary UM (31%). 14 metastatic UM (100%) over-expressed CD117. CD117 expression correlated with cell differentiation, anaplasia, nuclear atypia and UM thickness as well.

Conclusion
nm23 definitely participates in tumor progression, however, it is not considered to be a key metastasis regulator. CD117 over-expression in advanced UM and UM metastases confirms that mitotic cycle activation via tyrosine kinase receptors is one of the crucial tumor progression mechanisms.

Response after hyperthermic isolated hepatic perfusion with melphalan for metastatic uveal melanoma

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Background
Uveal melanoma preferentially spreads to the liver and carries a poor prognosis once disseminated disease is clinically detectable. To date there is no effective treatment of metastatic uveal melanoma.

Methods
Fifteen Swedish patients with uveal melanoma metastatic to the liver had a Karnofsky score of 80 or above and a tumour mass radiologically less than 50% of liver volume. The patients received hyperthermic (40°C) isolated hepatic perfusion with Melphalan 1 mg/kg body weight divided into two doses given 30 min apart. Median operative time was 6 hours (range 4–8 hours). One-third of patients had a significant haemorrhage post-operatively. Patients were confined to an intensive care unit for a median of 4 (range 1–24) days after perfusion. There were no deaths related to the procedure.

Results
Median follow-up after perfusion was 13 months (range 3–28 months). A total of 14/15 (93%) patients had either a complete (n=4) or a partial (n=10) response. Extrahepatic tumour recurrence became evident in half of the patients. Two patients died of progressive disease at 13 and 21 months after perfusion (17 and 23 months after diagnosis of metastatic disease).

Conclusion
This technique provided a high tumour response rate. Complications were significant in one third of patients but did not include deaths related to the procedure. A subset of patients may survive for two years or more after perfusion.

Applicability to surgically managed patients of the Helsinki University Central Hospital (HUCH) working formulation for staging metastatic uveal melanoma

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Purpose
To assess applicability to surgically managed patients of the Helsinki University Central Hospital (HUCH) working formulation for staging metastatic uveal melanoma (UM).

Methods
226 patients who died of metastatic UM were collected by the European Ophthalmic Oncology Group (OOG). Performance status, largest diameter of largest metastasis and serum alkaline phosphatase at diagnosis of metastases were available. The formulation is based on a multivariate model. Patients whose predicted survival is less than 6 months were assigned to stage IVc, those predicted to live between 6–12 months to IVb and those predicted to live over 12 months to IVa. Observed median survival was calculated.

Results
Of 201 patients managed without resection, 83 (41%) were stage IVa, 88 (44%) were stage IVb, and 30 (15%) stage IVc. Observed survival worsened with increasing substage ($P<0.0001$, log-rank test for trend). Observed median survival was 17.2 months for stage IVa, 10.0 months for stage IVb, and 4.2 months for stage IVc. Of 47 patients managed with surgical resection of metastases as part of treatment, 27 (57%) were assigned to IVa, 19 (40%) to IVb, and one to IVc. The substages did not differ from each other ($P=0.69$). Observed median survival was 26.7 months for IVa, 26.0 months for IVb, and 17.0 months for the single patient with IVc.

Conclusion
The working formulation does not differentiate patients with better prognosis if patients underwent surgery; conversely, it might be taken to provide evidence that surgery may be more effective than chemotherapy in managing metastatic UM.

Expression of human cancer-testis antigens, MAGE-A1, -A4, -C1 and NY-ESO-1 in primary human uveal melanoma

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Background
Metastatic disease in uveal melanoma remains untreatable, associated with late detection and resistance to conventional systemic therapies. Skin melanoma and many other tumours express specific cancer-testis (CT) antigens and vaccines that target these antigens can induce T-cell-mediated and humoral immune responses. We examined primary uveal melanomas for expression of CT antigens, to assess their potentially use as targets for uveal melanoma immunotherapy.

Methods
Paraffin-embedded samples of uveal (n=26), conjunctival (n=9), mucosal (non-skin) (n=8) and subungual/acral lentiginous melanomas (n=10) were assessed by immunohistochemistry for melanocyte differentiation antigens: gp100, Melan-A/MART-1, and tyrosinase, and the CT antigens: MAGE-A1, MAGE-A4, MAGE-C1 and NY-ESO-1.

Results
Melanoma differentiation antigens, gp100, Melan-A/MART1 and tyrosinase were consistently and highly expressed in all melanomas (>75% of cells); conjunctival melanomas showed reduced tyrosinase expression (<75% cells for ~60% tumours). Regardless of tumour type, CT antigens were generally expressed less frequently and at lower levels. Mucosal (non-skin) melanomas expressed all CT antigens, with MAGE-A1, MAGE-A4, MAGE-C1 and NY-ESO-1 in 45%, 20%, 50% and 70% of tumours respectively. MAGE-C1 and NY-ESO-1 expression was seen in 25% and 65% of subungual/lentiginous melanomas, and 10% and 20% of conjunctival melanomas; MAGE-A1 and -A4 were present in ~10% of these tumours. In contrast, uveal melanomas uniformly showed minimal or no expression of all CT antigens tested.

Conclusion
Uveal melanomas are clearly distinct from other melanomas, with very low or no expression of all CT antigens studied. This finding indicates that these melanomas, unlike skin melanomas (and many other tumours), are not suitable for CT antigen-based immunotherapy.

VEGF serum levels as a new marker for metastatic uveal melanoma

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Background
High levels of serum VEGF have been reported in cancer patients, especially in the metastatic stage of the disease. The purpose of this study was to examine the potential of VEGF serum levels to serve as a tumor marker in uveal melanoma patients. In particular, to compare the VEGF levels in metastatic patients before and after the detection of metastases.

Methods
Levels of serum VEGF were analyzed for 22 metastatic uveal melanoma patients, followed up every six months. The serum biomarker levels were measured using the ELISA method. A matched-pairs analysis was used to compare pre-metastases marker levels with those measured after detection of metastases.

Results
Of the 22 patients, 16 underwent brachytherapy and 6 were enucleated. The mean (±SD) VEFG levels in the pre- and post-metastatic phases were 355.6.1 ±229.1pg/ml and 455.0 ±273.6pg/ml, respectively, both above the level in our normal individuals (70–330pg/ml). There was no difference in the pre-metastatic VEGF levels of enucleated vs. brachytherapy treated patients. A matched pairs t-test showed a significant increase in VEGF serum levels in parallel with the development of metastatic uveal melanoma ($p=0.0094$).

Conclusion
VEGF serum levels are increased in uveal melanoma patients and rise significantly with the development of metastatic disease. Further study is warranted to identify the exact time course of this rise and to verify the effectiveness of VEGF as an early detection marker for metastatic disease.

Nucleolar size in choroidal and ciliary body melanomas and corresponding hepatic metastases

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Purpose
This study aimed to investigate the relationship between hepatic metastasis and the mean diameter of the 10 largest nucleoli (MLN) in uveal melanoma.

Methods
A cross-sectional histopathological analysis of 37 metastases (13 surgical or needle biopsies, 24 autopsies) and corresponding primary choroidal and ciliary body melanomas was conducted, using statistical tests appropriate for paired data. The largest nucleoli were measured from digital photographs of silver-stained sections along a 5mm wide linear field. Confounders considered were presence of epithelioid cells and microvascular density (MVD), counted as the number of discrete elements labelled by monoclonal antibody QBEND/10 to the CD34 epitope.

Results
Hepatic metastases had more frequent epithelioid cells ($p=0.0047$) and a higher MVD (median difference, 7.5 counts/0.313mm^2 more; $p=0.044$) than their corresponding primary tumours. Hepatic metastases, especially in autopsy specimens rather than surgical biopsies, tended to have a smaller MLN (median 3.6 lm) than the corresponding primary tumour (median difference, 0.55 lm; $p=0.066$). The MLN in hepatic metastases was not associated with presence of epithelioid cells and MVD. Overall survival after diagnosis of metastasis was comparable whether hepatic metastases had a large or small MLN ($p=0.95$), whereas a high MVD tended to be associated with shorter survival ($p=0.096$) among the 13 patients with known survival.

Conclusion
The results suggest that MLN is not a useful marker for assessing prognosis after diagnosis of hepatic metastasis from uveal melanoma.

Comparative proteomic analysis of uveal melanoma serological peptidome

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Background
A better understanding of molecular biology of uveal melanoma is needed to characterize uveal melanoma and aid in treatment design. Cancer cells release protein biomarkers into extracellular environment and some of these products can end up in the bloodstream, serving as potential serum biomarkers. We studied the variabilities of serum proteomic spectra in patients with uveal melanoma before and after operation and compared patients' spectra with those of healthy controls.

Methods
Magnetic affinity beads were used to capture serum peptides and matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometer were used to compile serum peptide profiles. The spectra were analyzed using ClinProTools™ bioinformatic software to screen potential biomarkers.

Results
A panel of 49 peptides were differentially expressed between spectra of uveal melanoma patients and controls, of which 33 peptides were of higher intensities in patient group and 16 peptides were of higher intensities in control group. Based on combined use of these potential markers, peptides with mean molecular masses of 1467 and 9289 Da provide high sensitivity (83%), specificity (100%) and accuracy rate (93.3%) together to discriminate between the two groups. At the time point of 6-month postoperatively, the levels of many detected differentially expressed peptides showed no statistical difference from those in the control group. Fibrinogen α–chain precursors were identified as potential UM markers.

Conclusion
We have shown that a convenient and fast proteomic technique, affinity bead separation and MALDI-TOF analysis combined with bioinformatic software, facilitates the identification of novel biomarkers.

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Uveal tumours

Session 5

Melanocytic tumours

Uveal melanoma with extrascleral extension: local treatment and survival

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Introduction
We have reviewed the outcome of patient with uveal melanoma and extra scleral extension treated by conservative radiotherapy or enucleation.

Patients and method
In the Curie Institute database 2,256 patients treated for uveal melanomaare registered between 2000 and 2007. We have made a retrospective review of patients with extrascleral statistical analysis was performed. Similar study was performed in the database of patients treated in Nice with proton beam.

Results
72 patients of Curie Institute presented extra scleral extension at diagnosis. 38 (52.8%) were treated conservatively (proton beam in 18 cases and iodine plaque in 20 cases) and 34 (47.2%) were treated by enucleation followed by external beam radiotherapy of the orbit in 28 cases. Median volume of extra scleral extension and clinical characteristics of the tumors will be described. Median follow up is 34 months. Survival at 5 years is 42% in enucleated patients and 79% in patients treated by radiotherapy. No tumor recurrence was observed in patients treated by radiotherapy. In a series of 23 patients with extra scleral extension treated in Nice 4 local recurrences were observed and treated by secondary enucleation but no orbital recurrence was observed.

Discussion
Conservative management of uveal melanoma with extrascleral extension did not cause worse survival or local recurrence in our series.

Conclusion
Conservative management with plaque or proton beam is an acceptable option in selected case of uveal melanoma with extrascleral extension.

Follow-up study in high-risk uveal melanoma patients

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Background
Uveal melanomas have a significant predilection for metastasis to the liver: up to 50% of patients will develop metastases. The liver is the sole or dominant site in more than 80% of them. Microscopic complete (R0) surgical resection of liver metastases improves survival to 22 months in very high selected patients. Despite aggressive therapy, survival is poor; the 1-year survival rate is 10%. Prognostic factors from the primary include tumor diameter and thickness, anterior location, extraocular extension, epithelioid cell type, molecular markers as monosomy 3 and gene expression profile. Early identification of a high-risk group of patients might allow early detection of metastases, and increase R0 liver surgery.

Methods
We began in October 2006 an intensive follow-up prospective study to detect early minimal lesions with liver MRI in asymptomatic high-risk patients. High-risk was defined by thickness >8mm or diameter >15mm, or extrascleral extension, or monosomy 3. Primary objective was to increase R0 liver resection rate from 10 to 30% (α risk=0.04 and β risk=0.05); secondary objectives were overall survival, metastasis-free survival, predictive value of MRI and liver functional tests (LFTs).

After treatment of the primary tumor, patients undergo liver MRI and serum samples/6 months, LFTs/3 months. MRI screening consists in T1, T2, T1 dynamic series with gadolinium injection and LFTs in total bilirubin, ALAT/ASAT, alkaline phosphatase, GGT, LDH. MRI suspect abnormalities lead to surgical procedure. Information document was sent to radiologists, MRI central review was conducted by Institut Curie radiologists.

Results
From October 2006 to March 2009, 85 patients were enrolled, median age 60 (32-83), sex ratio M39:F46. The median uveal tumor diameter was 19mm (11–26), median tumoral thickness 11.6mm (2.7–17), with retinal detachment in 65 patients, and extraocular spread in 7.

Local primary treatment consisted in proton beam therapy in 9 patients, enucleation in 76. Secondary enucleation was performed in 5 patients (2 for local relapse). The histological cell type was epithelioid in 18 cases, fusiform in 17, mixed in 41. Monosomy 3 (FISH) was present in 41/58 analysed enucleations.

Median follow up was 15 months. The metastasis-free survival rate was 78% (68.3–89.6). Two patients underwent enucleation for local relapse, 24 patients developed metastasis, 2/11 operated patients had R0 liver surgery (18%). To date, 6 patients died (5 from metastasis, 1 myocardial infarction) and 17 patients are alive with metastasis.

Conclusion

MRI and LFTs screening analysis will be presented with an updated follow up in the 85 available patients.

Predicting the prognosis of ciliochoroidal uveal melanoma by its clinical characteristics: a European Ophthalmic Oncology Group (OOG) study

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Background
Multicenter study for revision of the clinical tumour, node, metastasis (TNM) system of ciliochoroidal melanoma.

Methods
Data of 8,252 patients regarding tumour thickness, largest basal diameter (LBD), ciliary body involvement (CBI) and presence of extrascleral extension (EXE) were analysed. Categories were defined empirically by dividing data into blocks representing 2x2 and 3x3mm fractions. Size blocks with most similar survival were grouped; first on a randomly drawn subset of 60%, validated with the remaining 40%. Four T categories were constructed, to be as uniform in survival as possible and not to comprise of a large majority of cases. Presence or absence of CBI and EXE defined four subcategories a–d. Stages were generated by combining subcategories with most similar survival.

Results
Of the tumours analysed, 24% classified to T1, 34% to T2, 30% to T3 and 12% to T4, respectively. 10-year survival for the T categories were 90%, 78%, 59% and 40%, respectively ($P<0.0001$). The survival of patients in the four subcategories based on CBI and EXE differed significantly within each T category ($P=0.039$ for T1, $P<0.0001$ for T2–T4). EXE larger than 5mm carried a significantly worse prognosis than a smaller one ($P<0.0001$), and comprised subcategory T4e. The corresponding 10-year survival rates for stages I, IIA–B, IIIA–C were 88%, 80%, 68%, 45%, 28%, 10%, respectively ($P<0.0001$).

Conclusion
First evidence-based clinical classification and staging proposal for chiliochoroidal melanoma awaits implementation and outside validation.

Iris color: as a prognostic factor in uveal melanoma

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Background
Iris color has been suggested as a prognostic factor for uveal melanoma mainly in Nordic countries. In our country, or even in south Europe, there are no existing studies that supporting this theory. In a previous report we have found and inverse proportion of iris colour compared to Nordic countries, then presumably prognosis of our patients would be different. The purpose of the present investigation is to study iris colour as a prognostic factor in uveal melanoma in the Spanish population.

Methods
A three grades iris colour classification previously validated was applied to uveal melanoma patients. The iris colour was then analized as an independent prognosis factor for survival and compared to other known prognostic factors.

Results
Median age of the 346 studied patients with uveal melanoma was 62.3 years, 51.2% were males. The iris colour distribution was 39.1% brown, 42.2% hazel-green and 18.8% grey-blue. OR (Odds Ratio) was 1 for brown, 0.79 for hazel-green and 0.94 for grey-blue. Tumor shape, localization, largest tumor diameter, systemic extension, activity and size showed no statistically significantly related with the exception of the extra ocular extension. Kaplan Meier survival curves showed no differences among different iris colours.

Conclusion
Opposed to previous reports the most frequent iris colour in the present series was brown. Patients with hazel-green iris colour showed less risk to present uveal melanoma after grey-blue and brown. In the present study iris colour, as an individual factor, showed no relation to the survival of patients with uveal melanoma.

Postlaminar optic nerve invasion – a clinicopathological study of 46 enucleated specimens over a period of 11 years

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Purpose
To evaluate the outcome of patients with retinoblastoma and postlaminar optic nerve invasion.

Methods
To analyze the enucleated globes of retinoblastoma received in the histopathology laboratory over a period of 11 years (1997–2007). 45 consecutive patients with post laminar optic nerve invasion were analyzed. The details of onset of the disease, phenotype, age/sex ratio, family history, socio economic status of the patient, pre and post treatment findings and the follow up details were analysed.

Results
Out of 490 eyeballs of retinoblastoma, 45 eyes of 45 patients had post laminar invasion (9.38%). Median age at diagnosis was 2 years (range 3 months–27 years). The male:female ratio was 3:2. Out of 45 patients 36 patients had completed the required follow-up after systemic therapy. 3 patients received EBRT, 32 chemotherapy, 8 EBRT and chemotherapy and 2 patients nil treatment. 36 patients were alive on last follow-up (follow up ranging from 1 year to 11 years). 2 patients developed systemic metastasis, 2 developed orbital recurrence with one of them developing intracranial metastasis. 5 patients were lost to follow-up.

Conclusion
Post-laminar optic nerve invasion in retinoblastoma is a high risk histopathological feature necessitating neoadjuvant chemotherapy. Supplementation of the same and detailed systemic evaluation of the patients decreases their mortality from this life threatening condition.

Quality of life of uveal melanoma survivors and their family members

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Background
Growing attention is given in the last decades to the impact of cancer on the lives of cancer survivors and their family members (FM). The purpose of this study is to describe the quality of life (QoL) of uveal melanoma (UM) survivors and their FM as a factor of age, diagnosis, time since diagnosis, primary treatment, overall best corrected visual acuity (BCVA), and BCVA in the melanoma eye.

Methods
UM patients and FM coming for regular office visits were requested to fill in QoL questionnaires (patients: the EORTC QLQ-C30 and EORTC QLQ-OPT30 modules; FM: the Caregivers' Quality of Life tool, a 36-items self report questionnaire which includes 4 subscales regarding physical, psychological, social and spiritual well being). Independent demographic variables were also collected. Medical information was collected from patients' records.

Results
From January through August 2007, 232 of 294 patients and 113 of 145 family members completed the questionnaires. Patients' QoL was high and depended on the eye related QoL. In general, QoL of UM survivors' families appear to be better than that of other cancer survivors' families. A majority (73%) were highly distressed by the diagnosis and 64% by the treatment.

Conclusion
Patients with uveal melanoma and their FM are in need of psychosocial intervention. The intervention is needed mainly at the time of diagnosis. All patients and FM need information about physical and psychosocial implications of treatment in the short and long-term.

Socioeconomic deprivation and choroidal melanoma in Scotland

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Background
The adverse impact of socioeconomic deprivation on health and mortality is well recognised in the UK, particularly for health inequalities in Scotland. We wanted to evaluate this relationship regarding choroidal melanoma, to assess if deprivation had any impact on incidence or treatment.

Methods
All newly diagnosed patients with choroidal melanoma examined at the Regional Ocular Oncology Service at Tennent Institute of Ophthalmology, Glasgow, from 1994–2008 were included. Choroidal melanoma was diagnosed via clinical appearance and ultrasound findings. Home address postcode was used to determine the Scottish Index of Multiple Deprivation (SIMD) score and correlated with distribution of incidence and treatment modality.

Results
536 patients were identified. Mean age at presentation was 63.8 (SD=13.7) years. 54% were male, with 50.4% occurring in the right eye. No lesion exhibited bilaterally. Average wait from referral to first review at clinic was 17 days. 42.1% had a presenting visual acuity of 6/9 or better, with 28.8% being 6/60 or worse. There were 630 total treatments, including ruthenium plaque for 43.5%, proton beam for 22.5% and enucleation for 15.6% (7% primary enucleation). No treatment group was normally distributed ($p<0.005$) and there was no evidence of a difference between the median SIMD values between the treatment groups (Kruskal-Wallis $p=0.908$).

Conclusion
Socioeconomic deprivation was not found to be a significant factor for choroidal melanoma or subsequent treatment modality. This is particularly relevant in Scotland as optometric eye care is now free for all. Earlier detection could potentially reduce the enucleation rate.

Thursday
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Uveal tumours

Session 6

Melanocytic tumours

Characterization of three choroidal melanoma cell lines derived from FNAB of primary tumors with metastatic outcome

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Background
Our goal is to develop low-passage choroidal melanoma cultures which are stable for cytogenetic patterns and expression profiles found in primary melanomas that result in metastatic disease.

Methods
Fine needle aspiration biopsy (FNAB) of 59 primary choroidal melanomas was performed at the time of 125-I plaque placement (55 tumors) or immediately after enucleation (4 tumors). Cells obtained from the biopsies were analyzed by 500K Mapping Array and U133 plus 2.0 Expression Array and were prepared for cell culture. At passage 3, cell lines were evaluated on Mapping Arrays, Expression Arrays and by qRT-PCR.

Results
33 melanomas had chromosome 3 loss and 26 melanomas had chromosome 6p gain. Under the growth conditions employed, none of the 6p-gain melanomas successfully propagated. From monosomy 3 melanomas of patients who developed metastatic disease within 1.5 years of FNAB, three cell lines were propagated and were shown to be stable for the chromosomal aberration pattern found in the respective primary tumors. Each cell line had monosomy 3, 6q loss, 8p loss, multiple 8q gain and 16q loss in common. Each cell line had RNA expression profiles similar to the respective primary tumors for the twenty most over- and under-expressed genes from our comparative gene list. Sequence analysis of codon 209 of GNAQ in the three cell lines demonstrated one wild-type culture and mutations of Q209L or Q209P in the other two.

Conclusion
FNAB of primary choroidal melanomas resulted in highly characterized, low-passage cell lines which are stable for the cytogenetic patterns and expression profiles found in primary tumor cells and may be useful in studies of metastatic potentiation.

Relative genetic imbalance (RGI) between chromosome 8 and MYC copy number as an indication of survival in uveal melanoma

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Background
Amplification of the long arm of chromosome 8 has been correlated to metastatic death of patients with uveal melanoma; patients with the highest numbers of additional copies of 8q have significantly reduced disease free interval. The shortest region of overlap (SRO) within this region is 8q21-qter within which can be found the locus of the oncogene MYC at 8q24.1. MYC amplification is of interest as deregulation of the nuclear transcription factor has been correlated with increased cellular growth, proliferation and self-renewal, in addition to a poor level of differentiation. The objective of this study was to determine if increased MYC copy number compared to centromeric 8 (relative genetic imbalance or RGI) was a better indicator of prognosis.

Methods
Fluorescence in situ hybridisation (FISH) on 76 archival primary uveal melanoma samples was performed for CEP8 and MYC copy number.

Results
60% of samples showed a RGI, confirming MYC amplification and indicating that high levels of amplification for 8q will be missed using CEP 8 alone. RGI for MYC was found not to correlate with patient survival in the absence of an RGI for chromosome 3 and 8, but where an RGI for chromosomes 3 and 8 was present amplification of MYC further exacerbated the prognosis.

Conclusion
Evaluation of MYC is a useful indicator of prognosis but only adds value if additional copies are found in conjunction with other changes of chromosomes 3 and 8 as determined by FISH.

Sequential probing for subtelomeric arms of chromosome 6 and centromeric chromosome 3 in choroidal melanoma fine needle aspiration biopsies

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Background
To determine if the prognostic value of monosomy 3 testing in fine needle aspiration biopsies (FNAB) of choroidal melanoma can be improved by the inclusion of fluorescent probes specific for the subtelomeric regions of chromosome 6pq.

Methods
FNAB was obtained at the time of radioactive iodine-125 plaque placement. Slide smears of aspirates were sequentially probed for the subtelomeric regions of chromosome 6pq and the centromeric region of chromosome 3 and scored for the number of fluorescent signals in up to 300 nuclei per smear. Results were compared with high density mapping array findings.

Results
Technique of serial probing was feasible for samples. Results included patients with monosomy 3, 6p-gain, monosomy 3 and 6p-gain, monosomy 3 and 6q-loss, and normal signal pattern for both chromosomes. In a case where monosomy 3 and 6p-gain were detected concurrently, the aberrations were found to occur in the same nuclei and did not exist as two separate cell populations.

Conclusion
The inclusion of chromosome 6 testing allows for a positive finding for the presence of tumor in FISH-probed aspirates in which monosomy 3 is not detected. This provides better prognostic information for tumors with lower likelihood of metastatic outcome. The combined use of these FISH probes can identify homogeneity of tumors that contain hybrid monosomy 3 and 6p-gain signal pattern not addressed by microarray.

Chromosome 3 status in 500 eyes with uveal melanoma

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Background
Chromosome 3 is one of the genetic markers identified in uveal melanoma. Fine needle aspiration biopsy at the moment of plaque brachytherapy can provide an adequate sample for genetic testing.

Purpose
To evaluate chromosome 3 status in uveal melanoma.

Methods
500 melanomas underwent fine needle aspiration biopsy (FNAB) and micro-array analysis for chromosome 3 disomy (D), partial monosomy (PM), or complete monosomy (CM).

Results
There was D in 247 melanomas (49%), PM in 133 (27%) and CM in 120 (24%). Median tumor thickness (D vs PM vs CM) was 3.5, 4.0 and 4.6mm and ciliary body involvement was 5%, 12% and 19%, respectively. At 2 years follow-up, metastasis was 2%, 5% and 13%.

Conclusion
Chromosome 3 monosomy occurs in 51% of uveal melanomas by FNAB. Early data suggests uveal melanoma patients with chromosome 3 monosomy are older (median age 55 in D, 58 in PM and 60 in CM), have larger tumors, higher proportion of ciliary body location and a higher rate of metastasis. Genetic testing using fine needle aspiration biopsy can provide prognostic information in these patients.

In-vivo cytogenetic testing of uveal melanoma: seven years of clinical experience

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Background
Cytogenetic profile of uveal melanoma is a highly specific marker for life prognosis. In the past, cytogenetic prognostication was unfortunately limited to enucleated eyes or resected tumors. The aim of this study is to evaluate safety and efficacy of in-vivo transcleral fine needle aspiration biopsy (FNAB) used as a routine procedure for cytogenetic testing of posterior uveal melanoma.

Methods
One hundred twenty-two consecutive cases of posterior uveal melanoma (thickness >3mm) scheduled for I-125 brachytherapy were included in this prospective study. Patients underwent in-vivo 25-G transcleral FNAB just before applying the radioactive plaque. Sampled material underwent fluorescence in situ hybridization using standard procedure. Follow-up was longer than 24 months.

Results
Follow-up was 48 ±18 months (range 24–84 months). FNAB yielded sufficient material for FISH analysis in 101 of 122 cases (82.8%). Forty-seven cases had monosomy 3 (46.5%). Chromosome 6 co-detection was performed in the latter 39 patients. -3 and +6p resulted mutually exclusive in 35 cases (89.7%). Neither short and long term complications nor extrascleral extensions were documented during follow-up. Univariate Cox analysis showed metastatic disease to be strongly associated with monosomy 3 ($p<0.001$).

Conclusion
The use of in-vivo 25-G transcleral FNAB, in a routine clinical setting, appears a long term safe and effective procedure for cytogenetic prognostication of posterior uveal melanoma in patients undergoing I-125 brachytherapy.

Heterogeneity of gene expression signature in melanocytic uveal tumors sampled at two sites by FNAB

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Purpose
Determine the genetic heterogeneity of melanocytic uveal tumors sampled in two different sites by FNAB.

Methods
Two distinct samples from 39 melanocytic uveal tumors obtained by FNAB were analyzed by GEP for the presence of the Class 1 (favorable) of Class 2 (unfavorable) signature. GEP class assignment was performed using a weighted voting (WV) algorithm. Confidence regarding each classification was expressed between -1 (complete confidence in Class 1 assignment) through 0 (no confidence in either prognostic class assignment) to +1 (complete confidence in Class 2 assignment). We arbitrarily regarded cases with WV $\geq \pm 0.5$ as high confidence, WV $< \pm 0.5$ but $\geq \pm 0.2$ as medium confidence, and WV $< \pm 0.2$ as low confidence.

Results
Tumor thickness ranged from 1.8 to 12.0mm (mean=5.9mm, SD=2.8mm). Twenty-one tumors were categorized as Class 1 at each site, 13 were categorized as Class 2 at each site, and 3 were discordant. Two of 12 tumors with thickness ≤3.5 mm, 1 of 15 tumors with thickness >3.5 but ≤7 mm, and none of the 12 tumors with thickness >7mm exhibited discordant GEP results. Mean thickness of homogeneous tumors was 6.0mm (SD=2.9mm), and of heterogeneous tumors was 4.4mm (SD=1.8mm) (P=0.3, t-test).

Conclusion
The minority of the evaluated melanocytic uveal tumors exhibited GEP heterogeneity, and these tended to be smaller which suggests (not prove) that some Class 1 tumors eventually become Class 2.

Gene expression profile (GEP) class versus thickness of melanocytic uveal tumors evaluated by FNAB

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Purpose
Determine the relationship between GEP classification and thickness of melanocytic uveal tumors sampled by FNAB.

Methods
FNAB samples from 44 melanocytic uveal tumors were analyzed by GEP for Class 1 (favorable) versus Class 2 (unfavorable) expression signature. Relationship between GEP classification and tumor thickness confirmed by ultrasound was evaluated by cross-tabulation analysis and independent groups t-testing.

Results
Tumor thickness ranged from 1.8 to 12.0mm (Mean=5.6mm, SD=2.8 mm). Pre-FNAB diagnosis was choroidal melanoma in 29 cases, ciliary body melanoma in 10, and nevus versus melanoma in 5. Sixteen tumors were ≤3.5mm thick, 16 between 3.5 and 7mm, and 12 were >7mm thick. Twenty-five tumors were Class 2 by GEP while 19 were Class 1. Four of 16 tumors ≤3.5mm thick (25%), 8 of 16 tumors between 3.5 and 7mm thick (50%), and 7 of 12 tumors >7mm thick (58.3%) were Class 2. Mean thickness of Class 1 tumors was 4.6mm (SD=2.5mm) and of Class 2 tumors was 6.9mm (SD=2.7mm) (P=0.006, t-test).

Conclusion
The thicker a melanocytic uveal tumor, the higher the likelihood the tumor would be categorized as Class 2 (unfavorable) by GEP. Possible explanations for this relationship are: (1) some smaller tumors categorized as Class 1 become Class 2 as they enlarge; and (2) Class 2 tumors enlarge faster (on average) than Class 1 tumors; consequently being more frequently among larger tumors.

Identification of genetic and epigenetic alterations that may contribute to the pathogenesis of uveal melanoma

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Purpose
We investigated a panel of uveal melanomas (UM) for the presence of allelic losses at some chromosomal regions where structural abnormalities had previously been found, and the methylation status of TSGs supposed to be involved in UM pathogenesis.

Methods
Loss of heterozygosity (LOH) at chromosomal regions 1p36, 1p31.3, 3p (VHL, RASSF1A, FHIT), 3q, 9 (p21.2–p21.3) (CDKN2A), 10 (q23.2–q23.3) (PTEN), 13q14.2 (RB1) was investigated by PCR-based microsatellite analysis in 107 UM. Samples were also analyzed for the methylation status of VHL, RASSF1A, FHIT, CDKN2A and RB1 by methylation-sensitive restriction enzyme PCR. Clinical and histopathological parameters were analyzed together with genetic abnormalities.

Results
Monosomy 3 was detected in 48 of 107 tumors, and showed an association with the presence of epithelioid cells ($p<0.0001$) and ciliary body involvement ($p=0.001$). Methylation analysis discovered frequent methylation of RASSF1A (24%), predominantly in UM without monosomy 3. LOH at all 1p markers was found in 25 samples, and an association with extrascleral invasion of the tumor was determined ($p=0.01$). We detected infrequent hypermethylation of CDKN2A and LOH at 9p21.

Conclusion
We corroborate that monosomy 3 is the most common pathologic feature associated with aggressive UM phenotype. We suggest that deregulation of the RASSF1A may be involved in tumorigenesis in a significant proportion of UMs. We point out an association of large scale 1p deletion with extrascleral invasion of tumor, which is found to be independent of monosomy 3. Inactivation of CDKN2A and RB1 with promoter methylation or LOH is not the major mechanism of the pathogenesis in UM.

Transscleral white-light spectroscopy for assessment of melanin content in experimental choroidal lesions

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Background
To evaluate the feasibility of using transscleral white-light spectroscopy to estimate the content of melanin in a novel uveal melanoma phantom of ex-vivo porcine eyes.

Methods
Phantoms were made by injecting a suspension of gelatine, titanium dioxide, and natural melanin into the suprachoroidal space of 30 enucleated porcine eyes. The melanin concentrations used were 1mg/ml, 2mg/ml, and 3mg/ml, with 10 eyes in each group. The exact size and location of the phantoms were documented by B-scan ultrasonography and transillumination. White-light spectroscopy was performed with an optical fibre probe that exerted a fixed pressure on the outer scleral surface. Measurements were carried out across the phantom inclusion and on the opposite (normal) side of each eye. The absorption spectra were analysed using partial least squares regression.

Results
In phantoms with 1mg/ml, 2mg/ml, and 3mg/ml melanin, the largest basal diameters (mean ±SD) were 14.9 ±1.6, 14.6 ±1.5, and 14.3 ±1.0mm, respectively ($P>0.05$), and the largest thicknesses were 4.0 ±0.5, 4.4 ±0.7, and 4.5 ±0.5mm, respectively ($P>0.05$). Statistical regression modelling of the spectral data revealed that it was possible to correctly classify the phantoms according to their melanin concentrations in 84.4% of cases. The correct classification rate for phantoms with the lowest and highest melanin concentration was 99.2%.

Conclusion
The study demonstrates that transscleral white-light spectroscopy is a feasible diagnostic method for predicting with a high degree of certainty the content of melanin in choroidal lesions.

Association between gene expression profile classification and cytopathologic cell type of melanocytic uveal tumors evaluated by FNAB

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Purpose
Determine the relationship between gene expression profiling (GEP) classification and cytopathologic diagnosis of melanocytic uveal tumors sampled by fine needle aspiration biopsy (FNAB).

Methods
Forty-four melanocytic uveal tumors sampled by FNAB in at least 2 different sites were evaluated cytopathologically for melanocytic cell type and by GEP for Class 1 (favorable) versus Class 2 (unfavorable) signature. The relationship between GEP and cytology was evaluated by cross tabulation analysis.

Results
Cytodiagnosis for Class 1 tumors was epithelioid cell/necrotic melanoma in 6 cases, mixed cell/unspecified melanoma in 5, QNS in 5, spindle cell melanoma in 5, borderline in 3, and nevus in 1. Cytodiagnosis for Class 2 tumors was epithelioid cell/necrotic melanoma in 6 cases, mixed cell/unspecified melanoma in 6, spindle cell melanoma in 5, borderline in 1, and QNS in 1. Cytodiagnosis was non-melanoma/indeterminate in 9 Class 1 and 2 Class 2 tumors, and definite melanoma in 16 Class 1 and 17 Class 2 tumors. This difference wasn't statistically significant (P=0.081, Fisher exact test). Six of 44 tumors (13.6%) yielded insufficient specimen for cytodiagnosis while all 44 cases had a sufficient specimen for GEP.

Conclusion
Tumors classified cytopathologically as unequivocal melanomas were much more likely to be Class 2 by GEP while those classified as melanocytic nevus, borderline tumor, or QNS, were more likely to be Class 1. However, because this association did not reach statistical significance, cytology should not be used as a surrogate variable for GEP for prediction of metastatic risk in uveal melanoma patients.

Clinical relevance of genomic analysis of uveal melanoma

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Background
Approximately 50% of patients with uveal melanoma develop metastases, which are almost always fatal. The identification of such "high-risk" tumours requires clinical staging, histomorphological grading, immunophenotyping and genotyping of these tumours.

Methods
The 10-year experience of the Liverpool Ocular Oncology Centre (LOOC) using a variety of cytogenetic and molecular genetic techniques, including fluorescence in situ hybridisation (FISH), multiplex ligation dependent probe amplification (MLPA), microsatellite analysis (MSA), single nucleotide polymorphism (SNP) arrays and array chromosome genomic hybridisation (aCGH) in uveal melanomas is presented here.

Results
Over 800 cases of uveal melanoma treated at the LOOC have been analysed with respect to chromosomal 3 status. These genomic data have been correlated with clinical and histomorphological features and incorporated into a neural network, which produces a survival curve that is relevant to an individual patient. This information has enhanced clinical management and psychological counselling of patients.

Conclusion
Genomic analysis of uveal melanomas is important sub-typing these tumours into "high" and "low" risk types, with the former being potential candidates for clinical trials. Our studies may help to identify signalling pathways that may be targets for future therapies.

The p53 pathway in uveal melanoma

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Background
Although some genetic alterations are prognostic in uveal melanoma, the molecular mechanisms that contribute to UM development remain elusive. Activation of p53 is an important protective response to oncogenic stimuli that is disrupted in many human cancers by mutation or dysregulation. UM are reported to have wild-type p53. Two important regulators of p53 are MDM2 (promotes p53 degradation by ubiquitination), and MDMX (antagonizes p53 transcriptional activity). High expression of MDM2/MDMX is observed in tumors with wild type p53. Nutlin-3 is a small molecule that can interrupt MDM2-p53 interaction.

Methods
RNA and protein were isolated from adjacent choroid and UM of enucleated eyes. Gene expression was determined by real time RT-PCR and western blot. Growth of uveal melanoma cell lines 92.1, OCM1, OCM3, Mel290 treated with 0, 1, 5, or 10μM nutlin-3 for 1, 3, and 5 days was determined by cell counting.

Results
The expression of p53 was similar in choroid and adjacent UM. MDM2 was over-expressed in 8/14 UM samples and MDMX over-expressed in 8/24 UM samples, relative to choroid. The p53 downstream genes, p21 and MDM2, were upregulated in UM cell lines after nutlin treatment, suggesting restoration of p53 function. Individual UM cell lines showed different levels of growth inhibition after nutlin-3 treatment. Down-regulation of MDMX expression after nutlin-3 treatment correlated with nutlin-3 sensitivity of UM cell lines.

Conclusion
The p53 pathway may be compromised by over-expression of MDM2/MDMX in UM. Restoring p53 function by nutlin-3 disruption of MDM2-p53 interaction is an interesting therapeutic target for UM.

A novel oncogene mutation in uveal melanoma and its clinical relevance

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Purpose
To describe the clinical and pathologic features associated with mutation of the GNAQ oncogene in uveal melanoma.

Methods
GNAQ status was determined on 53 untreated uveal melanomas. Mutation status was analyzed for association with patient age, tumor size and location, histopathologic cell type, cytogenetic status, gene expression profile and disease-specific survival. Statistical analysis was performed using Medcalc® version 9.5.1.0.

Results
GNAQ mutations were present in 25 tumors and absent in 28 tumors. The only feature associated with mutation status was posterior pole tumor location (Fisher exact test, P=0.002).

Conclusion
GNAQ is by far the most commonly mutated oncogene described to date in uveal melanoma. GNAQ mutation does not correlate with features associated with tumor progression and, thus, probably occurs early in the pathogenesis of uveal melanoma. Most tumors with GNAQ mutations were located in the posterior pole, similar to the dose distribution of light on the retina, suggesting a possible link to ultraviolet light exposure.

KIT oncogene mutations in uveal melanomas

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Background
The abnormalities in RAS/MAPK signal cascade and BRAF and/or NRAS activation are of a great importance in the progression of many tumors. Tumors that over-express CD117 (receptor tyrosine kinase KIT) and represent c-kit 11th exon mutation are susceptible to glivec target therapy.

Aim
To investigate c-kit mutations in uveal melanomas (UM) with CD117 (KIT) over-expression and to establish the possibilities of target therapy.

Materials and methods
15 paraffin blocks of UM with CD117 over-expression were used to obtain DNA. PCR with c-kit 11th exon primers was performed, PCR products were subsequently purified and directly sequenced.

Results
In 3 of 15 UM (20%), c-kit 11th exon mutations were identified. These mutations represented deletions in 5' ends of c-kit 11th exons.

Conclusion
The presence of c-kit mutations in UM necessitate to extend the spectrum of investigation aimed to find mutations in c-kit different exons thus providing the possibility to apply target therapy with glivec.

Reduced autotaxin expression in uveal melanoma correlates with epithelioid cell type and predicts a poor prognosis

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Background
Gene expression profiling of uveal melanoma has previously identified reduced expression of autotaxin as predictive of poor prognosis. Autotaxin processes phospholipase D activity, which produces lysophospatidic acid (LPA) and autotaxin and LPA are implicated in tumour progression, invasion and metastasis. LPA acts as an extracellular, water-soluble lipid mediator with growth-factor-like properties, producing changes in cell morphology, motility and invasion as well as changes in protein synthesis that affects cell survival and growth factor production. Given the role that autotoxin is reported to have in cancer progression the observation of its reduced expression correlated with poor outcome is puzzling. Using Immunohistochemistry we studied a series of primary uveal melanomas for the localization of autotoxin.

Method
A series of 70 patients with uveal melanomas were investigated, and immunohistochemistry was performed on 5μm sections using autotaxin (KM105, Trans Genic Inc, Japan). Staining was considered positive when it was associated with an appropriate structure, cytoplasm, ECM or membrane.

Results
Autotaxin protein expression was strongest in uveal melanoma with a high spindle cell population, and lower in tumours with more epithelioid cells. Patients that had all cells staining had a median survival time of approximately 75 months compared to 46 months for those that had reduced autotaxin.

Conclusion
The results of this study confirm previous findings from our mRNA data study, and two other microarray studies. These studies demonstrate that autotaxin expression is associated with a less aggressive phenotype and a better patient prognosis in uveal melanoma.

Autotaxin expression in ocular tissue and uveal melanoma

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Background
Gene expression profiling has recently demonstrated underexpression of an enzyme called autotaxin, which apparently predicts class 2 uveal melanomas. This contrasts with overexpression in some carcinomas. This study undertook to assess the overall staining patterns of this enzyme by immunoperoxidase in 15 enucleated eyes with uveal melanomas. The results were correlated with FISH results for monosomy 3 (available in 14 of the 15 cases).

Methods
Immunohistochemical staining for autotaxin was performed on 15 globes using enhanced red alkaline phosphatase detection kit (Ventana).

Results
Positive staining for autotaxin (positive control: prostatic adenocarcinoma) consisted of a cytoplasmic blush and/or punctate cytoplasmic granules. Strong positivity was found uniformly in all layers of the retina in all 15 eyes. The non-pigmented ciliary epithelial cells, retinal pigment epithelial cells, corneal epithelium and smooth muscle of the ciliary body were also variably positive. The corneal stroma and sclera were uniformly negative.

Three cases were negative for autotaxin (0%), 1 showed scant staining (5%), and 11 showed variable staining in 10% to 100% of the tumor cells. Of the 4 negative/scant staining cases, 3 were monosomy 3 by FISH (no FISH results for fourth). Of the 11 positive cases, only 3 had monosomy 3.

Conclusion
1. Autotaxin is overexpressed in some malignancies but underexpressed in some uveal melanomas. 2. Immunoperoxidase staining for autotaxin may offer an economical way to stratify patients. 3. Additional work is needed to further classify the patterns of staining of this antibody, as experience is so far limited.

Next generation sequencing of biomarkers for uveal melanoma metastasis

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Purpose
Uveal melanoma (UM) is the most common form of adult onset primary malignant intraocular tumor with a significantly high incidence of loss of vision and a high degree of mortality associated with distant metastasis. Monosomy 3 is a biomarker for UM prognosis and predicts significantly increased risk of metastasis.

Methods
With this background, we performed a pilot experiment to obtain the mutation profile for all 116 cancer associated genes on chromosome 3 (tumor sequencing project, CGAP, NCI). We sequenced all exons in these genes in DNA isolated from UM tumors, with and without monosomy 3. The 776 coding exons of the 116 genes were captured by hybridization of fragmented genomic DNA to a custom designed, 385K microarray followed by washing, elution (Roche Nimblegen, IN), and pyro-sequencing on the GS FLX (Roche 454) platform.

Results
The sequencing results for 116 genes on chromosome 3 indicated presence of 771 nucleotide differences with respect to the Hg18 reference sequence. Of these 721 differences mapped back to known single nucleotide polymorphisms (dbSNP database). The remaining 50 differences included non-synonymous and synonymous changes as well as frameshift mutations in coding and flanking non-coding regions as well. These results are now being validated by Sanger sequencing.

Conclusion
Unique mutation profiles identified genes mutated in all UM as well as genes specifically mutated in UM with monosomy 3. The results translate basic cytogenetic observations into identification of clinically relevant biomarkers of metastasis and potential therapeutic targets in UM.

Should pathologists obtain informed consent prior to testing?

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Background
At the 2007 Meeting of the International Society of Ocular Oncology, there was a brief discussion about obtaining consent from patients with uveal melanoma prior to testing for monosomy 3. Monosomy 3 is a powerful prognostic marker, able to separate patients into two groups, one group with a very good prognosis, and one group that will likely die of disease. There is currently no treatment for those patients who are found to be in the poor prognosis group. Essentially, the laboratory physician is performing a test that will tell the patient: 1) you will probably die of this disease and: 2) there is nothing we can do about it.

Methods and results
We conducted an informal survey of local health care professionals. In our questionnaire, 24% of respondents said that they would not want to know the results of monosomy 3 testing. 94% of respondents said that the patient should be either asked or sign a legal consent form prior to testing.

Conclusion
These results should shock laboratory health care professionals who usually assume that a patient who presents to a doctor or to a hospital has given implied consent to testing. In Canada, implied consent is not a legal consent. It is our opinion that the specialty of pathology should begin to discuss the issue of consent for testing. Pathologists are in a critical position to communicate to clinicians, patients and the public at large the issues of informed consent: what are the risks (emotional, physical, legal, and economic), and what are the benefits of testing?

Thursday
10th September 2009

Uveal tumours

Session 7

Other uveal tumours

Mes(ect)odermal leiomyoma: diagnostic approach and management

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Background
Mes(ect)odermal leiomyoma is a rare benign intraocular tumor on which mostly only single case reports (nr: ~60), based on coincidental histopathological findings, have been published. Clear diagnostic or therapeutic guidelines have not been established yet.

Methods
We studied retrospectively 6 consecutive leiomyoma cases, all diagnosed by incisional biopsy and consequently observed or treated since 2001. We present their clinical features, differential diagnostic approach and management.

Results
Referral diagnosis of all cases was uveal melanoma. All tumors were well delineated and originated in the ciliary body (5) or anterior choroid (1). Mean thickness was 7.2mm (3.8–11.6), with low internal reflectivity and a supraciliary/-choroidal location on US examination (UBM/20/10 MHz). Suspicion of leiomyoma (5) or melanocytoma (1) had motivated incisional biopsy as a diagnostic approach. Management consisted of specific surgical excision (3) or periodic observation (3).

Conclusion
Mes(ect)odermal leiomyoma has distinct clinical features, justifying incisional biopsy before planning further management adapted to its benign nature.

Diagnostic transretinal 25-gauge biopsy of choroidal non-pigmented tumors

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Purpose
To report our experience with transretinal biopsy using a 25-gauge vitrector for diagnostic cytology and immunohistochemistry of choroidal tumors.

Methods
Ten patients (10 eyes) presenting with a choroidal lesion of indefinite origin on the basis of ophthalmoscopic and US examination, were included in this prospective, non-comparative study and underwent transretinal biopsy with a 25-gauge vitrector under local anesthesia.

The sample was centrifuged and then embedded in agar and processed into paraffin wax. All sections obtained from the wax-embedded block were stained by hematoxylin–eosin, periodic acid–Schiff and immunohistochemical reagents.

Results
Transretinal biopsy was diagnostic in 10 of the 10 examined eyes (100%). Retinal perforation did not require treatment or result in retinal detachment; subretinal hemorrhage occurred in 8 eyes (80%) and cleared spontaneously in all patients within two months. Vitreous hemorrhage occurred in 3 eyes (30%); in two patients a spontaneous resolution was observed within two months whereas one patient required vitrectomy.

Conclusion
Transretinal 25-gauge vitrector biopsy for choroidal non-pigmented tumors is a feasible and safe procedure and frequently yields diagnostic information relevant to treatment.

Metastatic tumors to the iris – clinical presentation and treatment

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Purpose
Study of the spectrum of the clinical presentation of iris metastases and response to the treatment.

Material and methods
Retrospective review of 30 cases (29 patients) of iris metastases examined in Lausanne.

Results
In the tumor Register of the University Eye Clinic of Lausanne, 361 cases of uveal metastasis are recorded. In 29 patients (8%), there was a localisation to the iris. This, was 7 men (24%) and 22 females (76%). The primary tumor was a breast carcinoma in 15 cases, pulmonary carcinoma in 5 cases, melanoma in 3 cases and various others tumors in 5 cases. The delay before treatment of the primary tumor, and occurrence of iris metastases, had a large spectrum of variability and in 4 cases, the diagnosis of the iris metastasis preceded the diagnosis of the primary tumor. Iris metastases were nodular in 17 cases (57%), and diffuse in 13 cases (43%). Intraocular pressure was above 22 mmHg in 8 cases (27.5%). The ciliary body was invaded in 28 cases (94%), choroidal metastases were present in the same eye in 22 cases (75%), and in the contralateral eye in 9 cases (31%). In two cases, vitreous metastases were present. Various therapeutic protocols were applied including external radiotherapy (17 cases), proton beam irradiation (7 cases), chemotherapy (2 cases), and enucleation (2 cases). The survival of patients varies from 0 to 30 months (average: 7.6 months).

Conclusion
Iris metastases are rare and occur mainly in advanced generalized metastatic diseases. They are frequently associated to metastatic location of the tumor to the choroid and to the contralateral eye, and can give rise to glaucoma. These tumors respond positively to external radiotherapy. The treatment is meanwhile palliative and the survival of the patients is limited.

Iris and ciliary body masses: gonioscopic and fluorescein angiographic studies, with new observations

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Purpose
Documenting findings in iris and ciliary body masses involving the angle with gonio-photography (GP) and fluorescein angiography (FA).

Methods
Consecutive case series.

Results
Ten cases were identified between June 2006 and August 2008. Age varied from 18 months to 45 years. Lesions involved angle and ciliary body in all cases, and additionally the iris in 9 cases. GP and FA were done using Retcam 2 and are described. Preoperative diagnosis correlated with histopathological examination in 9 cases, and was provisional in a single case. Final diagnosis included a single case of aberrant lacrimal gland tissue, 3 cases of iridociliary melanocytoma, a single case of granuloma and 5 cases of melanomas.

Conclusion
The use of GP and FA in iridociliary masses was helpful in differentiating melanocytoma from melanoma in all cases.

High-frequency ultrasound biomicroscopy role for the differential diagnosis of ciliary body and iris tumors

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Background
To correlate high-frequency ultrasound biomicroscopic (UBM) findings of iris and ciliary body tumors with clinical and histopathologic features.

Methods
16 patients were included in the study. All patients underwent a complete ophthalmic examination including slit lamp biomicroscopy and photography, and gonioscopy. High-frequency ultrasound biomicroscopy (UBM) was carried out using a 35 MHz commercially available device (Optikon, 2000). Trans-scleral resection (TSR) was performed in all patients. Histological examinations allowed definitive diagnosis.

Results
16 eyes from 16 patients were evaluated including 2 iris, 11 ciliary body and 3 cilio-choroidal tumors. All the ciliary body tumors and one cilio-choroidal tumor showed clinical signs of iris root invasion. One of the iris mass was pigmented, the other one was amelanotic and highly vascularized. Extrascleral extension was identified in two patients with cilio-choroidal tumors.

Ultrasound features were nodular masses with medium internal reflectivity in all eyes (100%), homogeneous structure in 7 eyes (43.75%), non homogeneous structure with microcysts in 8 eyes (50%) and macrocysts in only one eye (6.25%). The working diagnosis was melanoma in all cases except the iris amelanotic mass. Histopathological examination detected 2 nevi, 11 melanomas, 2 melanocytomas and 1 metastasis from breast cancer.

Conclusion
Results of our study reveal that high-frequency UBM can provide information about tumor morphology, ultra-sound structure, qualitative internal reflectivity, localization, local extension and growth patterns. However, the accuracy of high-frequency UBM does not allow a correlation between clinical, ultrasonographic and histopathological features. Therefore, the differential diagnosis between benign and malignant tumours is not possible using UBM.

Photodynamic therapy with Verteporfin for circumscribed choroidal haemangiomas using standard treatment parameters

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Background
Photodynamic therapy with Verteporfin (PDT) has evolved as the standard treatment for circumscribed choroidal haemangiomas. In most studies, parameters different to the standard treatment for age-related neovascularization have been used, usually with relatively high light energy. We report a series of patients treated with the standard parameters for PDT.

Methods
A prospective analysis of circumscribed choroidal haemangiomas treated with PDT at one institution. All patients were treated using standard parameters that were developed for the treatment of exudative age-related macular degeneration (6mg Verteprofin/m^2, light energy 50 J/cm^2, light intensity 600mW/cm^2 using a 689nm laser for 83s). The spot size was adjusted to the greatest linear diameter of the lesion without any safety margin. The treatment was repeated if no signs of regression were seen on clinical examination during follow-up.

Results
A total of 52 patients (35 male, 17 female, age 25–77 years, mean 51 years) were identified. Of these, 46 patients had a minimum follow-up of ≥3 months. In this group, baseline tumour diameter was 4.3–14.8mm (mean 8.4, median 8.0), tumour thickness was 0.9–3.8mm (mean 2.4, median 2.2) and visual acuity was between logMAR 2.3 and 0 (mean 0.63, median 0.3). At 3 months, visual acuity was between logMAR 2.2 and 0 (mean 0.1, median 0.1). At the final follow-up visit, tumour thickness was between 0–3.4mm (mean 1.8, median 1.3).

Conclusion
PDT with standard parameters is highly successful in treating circumscribed choroidal haemangiomas. Based on our results, modification of treatment parameters is not justified.

Photodynamic therapy for vasoproliferative tumors and capillary hemangiomas of the retina

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Purpose
To evaluate the results of Verteporfin photodynamic therapy (PDT) in vasoproliferative tumors (VPT) of the retina and retinal capillary hemangiomas (RCH).

Methods
In a retrospective case series, 6 VPTs in 5 eyes, and 3 RCHs in 3 eyes underwent PDT which was performed using intravenous Verteporfin. Eyes were evaluated for tumor regression, final best-corrected visual acuity (BCVA), and final retinal status.

Results
Patients were followed for a mean period of 7.1±3.9 months. Mean number of PDT sessions for each tumor was 1.33 (range 1–2). Overall, mean BCVA improved from 1.7 ±1.06 to 0.88 ±0.8 logMAR ($P=0.017$). Tumor thickness decreased from 3.53 ±0.83 to 1.73 ±0.73mm ($P<0.001$). Subgroup analysis revealed improvement in BCVA and tumor thickness in the VPT group ($P=0.04$). However, in the RCH group, there was no statistically significant improvement in BCVA ($P=0.43$) despite significant reduction in tumor thickness ($P=0.024$). A favorable outcome characterized by improved or unchanged visual acuity was achieved and the tumor regressed in all eyes. Subretinal fluid was absorbed in all eyes except for one eye with preoperative proliferative vitreoretinopathy.

Conclusion
Vasoproliferative tumors and retinal capillary hemangiomas can be treated effectively by Verteporfin PDT and a favorable outcome can be expected.

Photodynamic therapy salvage following anti-VEGF therapy for choroidal osteoma-associated choroidal neovascularization

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Background
Choroidal neovascularization (CNV) is a known presentation and complication of choroidal osteoma. CNV is reported in 9–31% of patients and can be symptomatic in the peripapillary and foveal locations. Therapeutic options include thermal laser, anti-VEGF medications, surgery, and verteporfin-mediated photodynamic therapy (PDT). We present our experience with persistent CNV leakage in choroidal osteoma that required PDT salvage for sustained control.

Methods
Retrospective case review and world literature review.

Results
A 14-year-old Caucasian female with a circumpapillary but juxtafoveal choroidal osteoma had a symptomatic peripapillary CNV lesion with subretinal fluid. Presenting acuity was 20/200. Off-label bevicizumab injections were administered over a 9-month course with transient reduction in subretinal fluid between the 6 injections. Full fluence PDT was performed with CNV inactivation and visual acuity of 20/25 at 6 months.

Conclusion
Single agent anti-VEGF strategies have been effective in limiting subretinal fluid leakage in osteoma-associated CNV lesions. In a subgroup of patients more durable control may be offered by combination or sequential treatment with PDT. Further multicentered studies are required to optimize management in this condition.

Correlation of fundus autofluorescence (FAF) characteristics of metastatic choroidal tumors with optical coherence tomography/scanning laser ophthalmoscope (OCT/SLO)

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Background and objectives
To correlate fundus autofluorescence (FAF) characteristics of metastatic choroidal tumors with optical coherence tomography/scanning laser ophthalmoscope (OCT/SLO).

Method
A retrospective review of 10 choroidal metastases in 9 patients.

Results
All tumors were amelanotic, though 8 exhibited surface pigmentation. FAF imaging revealed hyper-autofluorescence in areas of focal pigmentation and subretinal fluid with hypo-autofluorescent margins (n=5) corresponding to OCT evidence of retinal pigment epithelial (RPE) thickening and subretinal fluid. Loss of RPE was FAF hypofluorescent. FAF changed with tumor growth. OCT best revealed elevation of the RPE and retina, RPE thickening and folds as well as retinal detachment.

Conclusion
FAF-imaging best defined surface characteristics and tumor margins. FAF-hyper-autofluorescence correlated to focal hyperpigmentation, subretinal fluid and advancing tumor edges. Optical coherence tomography better demonstrated intraretinal findings (atrophy, subretinal fluid, increased and lost RPE). This study shows that FAF and OCT reveal unique tumor characteristics of choroidal metastasis.

Thursday
10th September 2009

Uveal tumours

Session 8

Uveal tumour case reports (2)

Thursday
10th September 2009

Uveal tumours

Posters

Experience with iris stromal cyst aspiration and alcohol washout

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Purpose
To evaluate the success and complications of aspiration and alcohol washout (AAW) technique for iris stromal cysts.

Methods
13 patients had cyst aspiration followed by alcohol washout for a mean of 3 minutes.

Results
69% had failed treatment prior to referral. Nine cysts regressed with one AAW. Two patients required 3 treatments each. Complications included cataract (2), inflammation (3), transient corneal edema (2), persistent corneal edema (1) and medically controlled glaucoma (1). All cysts remained regressed after a mean follow-up of 7.5 months.

Conclusion
Cyst aspiration with alcohol washout offers good control with few long-term side effects.

Précis
Iris stromal cysts requiring surgical intervention are challenging cases with a high recurrence rate. Review of 13 patients with cyst aspiration followed by alcohol washout revealed low recurrence and few side effects.

Ten cases of intraocular melanoma in Shizuoka Cancer Center in Japan

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Background
The Shizuoka Cancer Center opened in September 2002. Thus far, 10 patients with intraocular melanoma have been consulted at this center.

Methods
We assessed 10 patients who had intraocular melanoma in Shizuoka Cancer Center in the past 6 years and 7 months.

Results
The above patients were 7 male and 3 female patients, and their ages varied between 37 to 83 years (mean age 62.7 years). Choroidal melanoma was diagnosed in 9 patients, and ciliary body melanoma in 1. The observation period ranged from 1 month to 45 months. The tumors measured 8–16mm at the base and 8–13mm at the height. Before therapy, ^{123}I-iodoamphetamine single photon emission tomography (IMP-SPECT) was performed for 5 patients, and positive results were obtained in all these patients. Enucleation was performed in 8 patients, and carbon beam therapy, in 2. Nine patients are still alive. One patient (with ciliary body melanoma) died of lung metastases which developed after carbon beam therapy. The patients were followed up in echography of the liver, measurement of the serum 5-S-cystein DOPA (5SCD) level, magnetic resonance imaging and computed tomography after the primary therapy. The serum 5SCD level was occasionally found to be elevated because of sunburns and the consumption of specific foods and drinks.

Conclusion
In Japan, the numbers of intraocular melanoma are very few. In Shizuoka Prefecture (duration of sunshine is long in Japan), the incidence rate was 1.4/2 million persons/ one year. However, we must observe these clinical courses carefully.

Human uveal melanoma cells inhibit the immunostimulatory function of dendritic cells

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Background
Dendritic cells (DC) are critical for inducing anti-tumor immunity. Recent studies suggest that tumor may evade immune destruction by inhibiting DC function. In this study we investigated the effect of uveal melanoma cells on human DC with respect to surface antigen expression, cytokine production, and T cell activation.

Methods
Dendritic cells were generated by culturing normal human peripheral blood mononuclear cells in the presence of GM-CSF and IL-4. On day 5 of culture, DC were exposed to human uveal melanoma cells (OCM-1, OMM-1, 92-1) for 24 hours and then purified using magnetic beads. Maturation of DC was accomplished by TNF-α. The phenotype and apoptosis of DC were analyzed by flow cytometry. Allogenic human T cells from healthy controls were cultured with DC exposed to human uveal melanoma cells for 24 hours, and T cell proliferation responses were measured.

Results
The expression of DC markers (CD1a, CD83), MHC class I, MHC class II, and costimulatory molecules (CD80, CD86 and CD40) decreased in DC exposed to human uveal melanoma cells. Moreover, exposure to uveal melanoma cells led to apoptosis of DC, as shown by 1.5-fold increase in surface phosphatidylserine using Annexin-V staining. Finally, DC exposed to uveal melanoma inhibited the proliferation of allogenic human T cells in mixed lymphocyte reaction.

Conclusion
These findings suggest a mechanism by which uveal melanoma escape immune elimination and have significant implications for the immune therapy utilizing DC for patients with uveal melanoma in the future.

Friday
11th September 2009

Retinal tumours

Session 1

Retinoblastoma

Retinoblastoma in children born before 40 weeks gestation

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Background
The diagnosis of retinoblastoma early in life is associated with higher rates of bilaterality and macular involvement of tumors early with later involvement of the peripheral retina. Furthermore, these patients are most likely to have been diagnosed as a result of screening due to a family history of retinoblastoma. Because little has been reported on patients born before term, the purpose of this study is to describe the demographics and clinical features of patients born pre-term who were diagnosed with retinoblastoma.

Methods
A retrospective study of patients from two tertiary referral centers. Life-table analysis was used to calculate ocular survival.

Results
Forty-eight patients were identified with retinoblastoma who were born before 40 weeks gestation (median gestational age 35.7 weeks). Leukocoria (57%) exceeded screening for family history (21%) and strabismus (13%) as the most common reason for detection. Twenty-seven (56%) patients presented with unilateral retinoblastoma. Fifty-four (78%) affected eyes presented with macular involvement, 39 (57%) of which involved the foveal center. Both eyes were salvaged in 28 (59%) patients, and one eye was salvaged in 19 (40%) patients through a median 18.3 months follow-up. No patient died. One patient developed a secondary non-ocular tumor of the pineal gland.

Conclusion
The clinical features of retinoblastoma patients born pre-term are similar to reported characteristics of patients born at term. As with full-term infants, screening plays an important role in the early diagnosis of retinoblastoma.

Role of fluorescein angiography in the management of intra-ocular retinoblastoma

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Purpose
To evaluate the indication of fluorescein angiography in the management of retinoblastoma.

Patients and methods
Between January 2007 and April 2009, 60 patients had a fluorescein angiography performed at presentation and at various time points of their follow-up.

Results
Characteristic angiographic features of the anterior segment and fundus will be presented.

Conclusion
In our experience, fluorescein angiography turned out to be of interest 1) to better characterize the ABC grouping at diagnosis, 2) to detect tumor recurrence during follow-up, and 3) to differentiate recurrence from radiation-induced changes following brachytherapy or external beam radiotherapy.

Brain abnormalities on MRI in retinoblastoma patients

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Background
Although pineoblastoma is the most important brain abnormality associated with hereditary retinoblastoma, recent studies suggested a similar association with pineal cysts. Mental retardation, developmental delay and congenital brain anomalies are also reported in these patients, mostly in 13q deletion syndrome. In this retrospective study the spectrum of brain abnormalities on MRI in retinoblastoma patients are evaluated.

Methods
Between 1989 and 2009 MRI of the brain of 188 retinoblastoma patients were evaluated for tumors, structural anomalies, myelinisation and coincidental findings. Clinical records were reviewed for tumor side, heredity and presence of 13q deletion syndrome. MR images were reviewed by two radiologists in consensus.

Results
Our hereditary group contained 102/188 patients (54.3%, bilateral and unilateral patients with proven RB1-germline mutation). Eight patients were diagnosed as 13q deletion syndrome. On MRI 27 brain abnormalities were detected. Five pineoblastomas were detected, all in hereditary retinoblastoma patients (overall incidence 2.7%; 5.8% in hereditary subgroup). Ten pineal cysts were detected (overall incidence 5.3%; 2.3% in hereditary and 7.8% in non-hereditary subgroup). Other (structural) brain abnormalities only occurred in combination with a 13q deletion syndrome.

Conclusion
Pineoblastoma is the only finding associated with hereditary retinoblastoma. Our incidence for pineal cysts on MRI was higher than reported in literature (1.5%–4.3%). Most pineal cysts presented in non-hereditary retinoblastoma patients. There is no further indication for brain imaging in retinoblastoma patients other than pineoblastoma.

Diagnosis of retinoblastoma: how good are referring physicians in 2009?

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Background
To evaluate accuracy of the referring diagnoses of retinoblastoma to a tertiary cancer referral center.

Methods
Retrospective chart review. Of 352 retinoblastoma-related patients seen by the ophthalmic oncology service during a 4-year period from January 1 2004 to October 21 2008, 111 were referred with a suspicion of new retinoblastoma and were included in the study. Fundus photographs, gender, family history of retinoblastoma, initial symptoms, age, initial and referring physicians' specialty (e.g. pediatrician, general ophthalmologist, retinal specialist) and their suspected diagnoses were recorded.

Results
Of 111 patients, 62% had retinoblastoma and 38% did not. Persistent fetal vasculature (PFV) and Coats' disease were the most common simulating lesions accounting for 31% and 29% of the simulating lesions respectively. Other simulating lesions included infrequent cases of rare conditions such as primary ocular teratoma, a retinal pigment epithelial tumor, and astrocytic hamartoma.

Conclusion
In 2009 retinoblastoma continues to present a diagnostic dilemma. There has been limited improvement in the rate of correct diagnosis in the United States in the last 15 years. There has however been a change in the composition of misdiagnosed lesions with rare conditions accounting for more than 1/3 of cases. Attention to age, family history, laterality and presenting signs such as globe size can aid diagnosis of retinoblastoma.

Angiographic findings in Coats' disease

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Purpose
To evaluate the fluorescein angiographic features and peripheral non-perfusions in Coats' disease.

Methods
Retrospective evaluation of fluorescein angiography in 39 consecutive eyes with Coats' disease.

Main outcome measure
Peripheral non-perfusion in Coats' disease detected on fluorescein angiography.

Results
The mean age at diagnosis was 5 years (range 1 to 39 years). The referring diagnoses included Coats' disease (17 patients, 48%), retinoblastoma (6, 17%), retinal detachment (3, 9%), and others (9, 26%). There was iris neovascularization (3, 8%), and ectropion uvea (1, 3%). Clinically, the posterior segment revealed telangiectatic vessels (35, 90%), aneurysmal vessels (4, 10%), and peripheral non-perfusion (2, 5%). The angiographic findings included telangiectasia (38, 97%), light bulb and microaneurysms (38, 97%), retinal non-perfusion (39, 100%), far peripheral contiguous non-perfusion (30, 77%) with demarcation line (23, 59%), mid-peripheral non-perfusion (33, 85%), and arterio-venous shunting (38, 97%). All findings were concentrated in the temporal quadrants.

Conclusion
Coats' disease commonly shows angiographic features of far peripheral non-perfusion near the ora serrata in the regions of classic telangiectasia, mostly in the temporal quandrant.

Treatment of unilateral retinoblastoma: results of a prospective study in Argentina

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Background
Adjuvant therapy of patients with risk factors on pathology in retinoblastoma remains controversial. We report the results of a prospective study on 106 patients (2002–2007).

Methods
Candidates (n=16) for eye salvage were offered chemoreduction. Those without possibilities for eye preservation were enucleated (n=89). Patients with intra-retinal (n=8), prelaminar optic nerve (n=5), choroidal (any degree) (n=37) and those with less than 20% of post-laminar optic nerve invasion (PLONI) without concomitant full choroidal or scleral invasion risk factors (n=11) did not receive adjuvant therapy. Those with PLONI and risk factors (massive choroidal, scleral or deeper invasion (n=21) and those with invasion to the resection margin (n=5) or isolated scleral invasion (n=2) received 4 cycles of carboplatin 500 mg/m^2/days 1 and 2 together with etoposide 100 mg/m^2 days 1-3; alternating 4 cycles of cyclophosphamide 65 mg/kg, idarubicin 10 mg/m^2 and vincristine 1.5 mg/m^2. There was only one patient with metastatic disease in the CNS and received palliative care.

Results
The 5-year pEFS is: 0.94. 5 relapses occurred. CNS (n=3) and all died of disease. Systemic (n=2) and 1 of them survived after ASCR. Pathology risk factors of relapsing patients included: PLONI n=2, isolated focal choroidal invasion n=1, tumor at the resection margin of the optic nerve n=1, CNS metastasis n=1. 7/16 eyes with preservation attempt were preserved.

Conclusion
Patient survival was excellent. After tailoring therapy to risk factors, 60% were spared from adjuvant treatment. For patients with very high risk features, our intensive regimen was highly efficacious.

Retinoblastoma in Egypt: a 5 year review of unilateral and bilateral cases: clinical spectrum and management

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Purpose
To determine the patterns of presentation, staging, management and globe salvage in children with retinoblastoma at two major referral centers in Egypt.

Methods
Retrospective chart review. Collected data were analyzed using SPSS 11 system.

Results
There were 158 unilateral and 143 bilateral cases. Mean age of presentation was 26.5 and 10.3 months. Leukocoria was the commonest presenting symptom. Most unilateral cases were advanced at presentation. Chemotherapy using carboplatin and vincristine were used in 43 unilateral and 105 bilateral cases in addition to focal therapy. Enucleation was used as a primary treatment in 94 (59.5%) unilateral and 93 (41.9%) eyes of bilateral cases. Tumor control was achieved in 40 (25.3%) unilateral and in 117 (40.9%) eyes of bilateral cases.

Conclusion
Unilateral RB was often advanced at presentation necessitating enucleation. Bilateral cases present often with advanced disease in one eye. Ocular salvage with chemofocal therapy is improving in Egypt.

The survival and visual outcome of bilateral retinoblastoma in Taiwan

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Background
In this retrospective study, we focused on the bilateral retinoblastoma cases and aimed to describe the survival characteristics and visual prognostic factors of these patients in Taiwan between 1978 and 2009.

Methods
A retrospective chart review of bilateral retinoblastoma patients treated at Chang-Gung Medical Center, Taipei, Taiwan, from January 1978 to April 2009 was performed. The demographic and ophthalmological data, clinical classification, treatment methods, survival rate, visual outcomes, and family history were recorded.

Results
A total of 31 patients (62 eyes) were included in the study, with a mean follow up of 67.23 months. The mean patient age at the time of diagnosis was 20.13 months (range 1.63–62.5). The most common presenting signs were leukocoria (56.5%), blurred vision (33.9%), elevated intraocular pressure (25.8%), proptosis (22.6%), and strabismus (17.7%). Only 2 of 31 cases (6.5%) were familial, and 8 patients had Rb1 gene mutation. Most eyes were classified as group E (79.0%) by International Classification of Retinoblastoma. The most common sites of extraocular invasion included orbit (37.1%) and central nervous system (33.9%). Only one eye developed secondary malignancy in the previously radiated orbit. The mortality rate of our bilateral retinoblastoma patients was 41.9%, with a mean age of 40.87 months (range 25.3–68.0) and a mean expired time after diagnosis of 18.69 months (range 5.27–52.33). In 23% of these cases, parents had refused the treatment suggested by the doctors. Visual acuity could be measured in 15 patients (20 eyes), and 11 eyes were no light perception, while 5 eyes had visual acuities of 20/40 or better. Clinical classification and macular involvement were the prognostic factors indicating the visual outcome.

Conclusion
The survival rate of bilateral retinoblastoma in Taiwan was lower than that in the developed countries. The proportion of patients' parents refusing treatment in Taiwan is high. The clinical factors that predicted visual outcome were clinical classification and macular involvement.

Outcomes of A + B tumours – do familial/non-familial eyes behave differently?

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Background
There is some suggestion that there is a difference in clinical course and treatment response between familial and non-familial cases with Group A and B retinoblastoma. The aim of this study was to report treatment results for Group A and B retinoblastoma, and compare outcomes for familial and non-familial cases

Method
22 familial eyes (2 treated with laser/cryo alone, 20 with chemotherapy and laser/cryo) and 21 non-familial eyes (2 treated with chemotherapy alone, 2 with laser/cryo alone and 17 with chemotherapy and laser/cryo) with a minimum follow-up of 1-year post treatment were included.

Results
59% of familial eyes and 11% of non-familial eyes developed new tumours. The rate of recurrences was similar for both groups. Familial cases were diagnosed at mean age of 3.7 months (range 7 days to 17 months) and mean duration to completion of active treatment was 13 months (range 1 to 38 months). Non-familial cases were diagnosed at mean age 10 months (range 10 days to 21 months) and mean time to completion of treatment was 7 months (range 1 to 24 months). No eyes required enucleation. 1 non-familial case required several salvage treatments. All other recurrences were successfully treated with laser/cryo or plaque therapy. No familial cases were registered visually impaired, but 1 non-familial case was registered blind. The majority had driving standard vision or better.

Conclusion
Familial and non-familial A + B tumours behave differently but final outcomes were excellent in both groups. Familial cases took longer to achieve remission, and showed a higher incidence of new tumours.

Eye salvage rate in retinoblastoma: a comparison between the Reese Ellsworth classification and the IIRC classification system

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Purpose
To analyze the eye salvage rates in Indian children with retinoblastoma and to compare the predictive capability of the Reese-Ellsworth and International Intraocular Retinoblastoma classifications.

Study design
Retrospective case series.

Patients and methods
Patient records from January 2002 to December 2005 were reviewed for tumor characteristics, age of patients, laterality, treatment given etc. Tumors were classified according to Reese-Ellsworth classification system as well as IIRC and the eye salvage rates were compared between 2 systems.

Results
Two hundred and seventy one (271) eyes of 206 patients were included. Tumor involvement was unilateral in 126 cases and bilateral in 80 cases. 15 eyes enucleated elsewhere were not included in the study. The mean age at presentation was 23.54 months (range 0–105 months). Hundred and seventy six (64.7%) eyes had IIRC D and E disease at presentation. Hundred and seventy-four eyes (64.2%) had stage V disease by Reese-Ellsworth classification. By IIRC classification, 100% of group A (n=15), 97% of group B (n=33), 76.7% of group C (n=43), 20.6% of group D (n=63), and 0.9% of group E (n=101) were saved. Eye salvage rates in Reese-Ellsworth stages were 100% in class Ia (n=11) and Ib (n=5); 92.3% in class IIa (n=13) and 100% in class IIb (n=6); 100% in class IIIa (n=12) and none in class IIIb (n=8); 63.6% in Iva (n=11), and 73% in class IVb (n=26); and 5.9% and 25.8% respectively for Va (n=101) and Vb (n=62).

Conclusion
The poor predictability in terms of salvage rates by Reese-Ellsworth staging shown in this study, especially in advanced cases suggests that adoption of IIRC system is warranted since it has better predictability.

Children's Oncology Group (COG) clinical trials in retinoblastoma: an update from the Children's Oncology Group

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The management of children with retinoblastoma requires a multidisciplinary approach. There is a long and successful history of prospective clinical trials involving several disciplines among pediatric oncologists in cooperative groups. The lack of a cooperative effort to address retinoblastoma provided an impetus to form the Retinoblastoma Disease Committee when the COG was formed in 2001. Several trials are now open. One of the controversial issues remains the definition of histopathologic high-risk features in enucleated eyes in children with unilateral disease. A prospective trial to address this issue with a central pathologic review was initiated with national and international participation. Two-thirds of the accrual goal has already been achieved. With the wide acceptance of the international staging system a clinical trial to asses the impact of only carboplatin and vincristine in children with B disease is evaluating the efficacy of this regimen in preventing recurrences. An aggressive approach with 6 courses of higher dose carboplatin (28 mg/kg) with vincristine/etoposide plus 3 doses of subtenon carboplatin is being evaluated in children with group C and D disease. Another clinical trial for patients with metastatic disease is open with both national and international participation. This study involves high-dose chemotherapy and stem cell rescue, and radiation therapy tailored to the location of the disease. These open trials with active participation from ophthalmologists, pediatric oncologists, radiation oncologists and ophthalmic pathologists bodes well for the conduct of future prospective clinical trials in children with retinoblastoma as new and innovative clinical strategies are discovered.

Japan retinoblastoma group study: novel local chemotherapies can reduce the burden of systemic chemotherapy to achieve eye preservation without EBRT

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Background
Two local chemotherapies, ophthalmic arterial injection and vitreous injection of Melphalan were developed in our group, first as salvage treatments after external beam radiotherapy (EBRT), led to significant improvement of ocular survival of eyes with refractory and/or relapsed tumours. In 1999, systemic chemotherapy was introduced, expected to replace EBRT. There are increasing reports suggesting systemic chemotherapy also induces second cancer.

Hypothesis
Our local chemotherapies may decrease the burden of systemic chemotherapy to achieve eye preservation without EBRT.

Purpose
To evaluate the efficacy of our new conservative treatment strategy using possible reduced cycles of chemoreduction with CEV regimen followed by intensive local treatments including local chemotherapies, transpupillary thermotherapy, and brachytherapy.

Results
Between 2001 and 2007, 125 eyes of 86 newly diagnosed patients (60 bilateral and 26 unilateral) were enrolled in this study. The median cycle number of systemic chemotherapy needed for eye preservation was two. Ocular salvage rate without EBRT was 75%. Using International Classification System, it was 100% in Group A, 81% in Group B, 72% in Group C, and 50% in Group D.

Conclusion
This new strategy is successful in most cases decreasing the need of EBRT, enucleation and systemic chemotherapy. Outside of this study, we have case series of patients treated only with local chemotherapies and other local therapies, suggesting local chemotherapies can replace both systemic chemotherapy and EBRT. We will go to the next study to evaluate efficacy of the conservative treatment only with local therapies.

The results of treatment in patients with high risk (HR) retinoblastoma (RB)

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Background
In order to improve DFS we performed a HDCT followed by autoPBSCT in pts with HR RB.

Methods
From 2001 to 2008 16 pts (8 female, 8 male) with HR RB were treated. The median age was 32 mos. Two pts had bilateral RB (1- orbital and 1-prechiasmatic involvement). HR was defined as microscopic tumor after enucleation (stage II, n=8), regional extension (stage III, n=4): orbit (n=3), regional lymph nodes (n=1); metastatic disease (stage IV, n=4): multiple lesions (n=1), prechiasmatic lesion (n=3). The treatment included 4 courses CT including cyclophosphamide, VP-16 and carboplatin, surgery and external beam RT at a dose of 50 Gy, HDCT by busulfan and melphalan followed by autologous PBSCT. 12 pts received autologous PBSCT.

Results
One pt (st. III) died from Klebsiella pneumonia sepsis. Three pts died (n=2 relapsed in CNS; n=1 in bone, BM, testis and lymph nodes). Eight pts are alive with a median period of follow-up of 55 mos. EFS and DFS were 62% and 66%. Three pts refused to receive HDCT. Two out of 3 (n=2 prechiasmatic lesion) relapsed in CNS and died. One with st.II is alive with free disease. One pt with orbital disease progressed on treatment and died. Nobody out of metastatic disease is alive.

Conclusion
HDCT followed by auto PBSCT improves results of treatment for stage II and III in HR RB patients. It is necessary search for new approaches in treatment metastatic disease Rb.

Multiple-failure intraocular retinoblastoma can be cured by cyclosporine-modulated chemotherapy with focal cryo/laser therapy

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Background
We previously reported that chemotherapy modulated by cyclosporine A, which inhibits multidrug resistance P-glycoprotein, cures 77% of newly diagnosed children with Group C, and 23% with Group D International Intraocular Retinoblastoma Classification (IIRC) eyes. We assessed the success of this protocol for previously treated relapsed eyes.

Methods
Since 1992 we have treated 21 eyes in 19 children who failed the following treatment modalities: chemotherapy (6), radiation (2), chemotherapy/plaque (1), chemotherapy/radiation (9), chemotherapy/radiation/plaque (2), radiation/plaque (1), each combined with extensive focal therapy. Short-infusion high-dose cyclosporine with carboplatin-etoposide-vincristine, with tumor consolidation by focal cryo/laser therapy, was administered as salvage therapy. Subsequent external beam radiation or enucleation were considered failures.

Results
Event-free eye salvage rate was 62% (13/21). The 12 successfully salvaged children (13 eyes) had useful vision 0.5, 0.5, 2.8, 4.8, 5.6, 5.7, 9.3, 11.2, 12.4, 12.7, 12.9, 16.1, and 16.8 years (median follow up 9.3 years) after salvage therapy. Of the failures, 4 children had a second-eye enucleation, 1 child had both eyes enucleated, 1 child had a first eye enucleated, and 1 previously unirradiated child retained the remaining eye after radiation. All children tolerated the cyclosporine-modulated chemotherapy with acceptable hematopoietic toxicity and no nephrotoxicity, neurotoxicity or ototoxicity, despite previous heavy chemotherapy.

Conclusion
Children relapsing after chemotherapy, plaque and radiation, who would otherwise be blind or radiated, may be cured by cyclosporine-modulated chemotherapy/focal salvage therapy. Cyclosporine was the difference between the failed primary therapy and successful relapse therapy, and may have reversed multidrug resistance.

Hypoxic retinoblastoma tumor targeting: use of periocular delivery of 2-deoxy-D-glucose

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Background
The purpose of this study was to evaluate the efficacy of periocular 2-deoxy-D-glucose (2-DG) delivery in targeting hypoxic cells in retinoblastoma tumors. To this aim, hypoxic cells were labeled by immunohistochemistry and tumor control was assessed by using varying dosages of 2-DG, a glycolytic inhibitor.

Methods
The study protocol was approved by the University of Miami, IACUC. Twenty-five 17 week-old $LH_{BETA}T_{AG}$ transgenic retinoblastoma mice were divided into 5 groups and received periocular injections to right eyes of (a) saline, (b) 2-DG (62.5mg/kg), (c) 2-DG (125mg/kg), (d) 2-DG (250mg/kg) or (e) 2-DG (500mg/kg). Mice received 60mg/kg of pimonidazole (10mg/ml) via intra-peritoneal injection two hours before enucleation. Eyes were enucleated at 20 weeks of age, snap frozen and analyzed for hypoxic regions and residual tumor.

Results
Tumor hypoxic regions decreased in all 2-DG treated groups. The group treated with the lower dose of 2-DG (125mg/kg) showed a decrease of 40% ($P<0.01$) in hypoxic regions while the group treated with the highest dose of 2-DG (500mg/kg) showed a decrease of 97% ($P<0.01$) in comparison with the saline controls. A marked decrease in tumor burden was also observed in the groups receiving higher doses of 2-DG (250 and 500mg/kg) in comparison with controls ($P<0.05$).

Conclusion
Periocular delivery of glycolytic inhibitors is effective in targeting hypoxic regions within advanced retinoblastoma tumors and in decreasing tumor burden. Periocular, focal delivery allows for direct localization of the drug and is important for limiting systemic toxicities.

Focal, periocular delivery of 2-deoxy-D-glucose as an adjuvant to chemotherapy for treatment of advanced retinoblastoma: evaluation in a murine transgenic retinoblastoma model

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Background
The purpose of this study was to evaluate the efficacy of periocular 2-deoxy-D-glucose (2-DG) delivery in enhancing retinoblastoma tumor treatment. Tumor control was assessed by using combination therapy of carboplatin, a chemotherapeutic agent, and 2-DG, a glycolytic inhibitor.

Methods
The study protocol was approved by the University of Miami, IACUC. Thirty 17 week-old $LH_{BETA}T_{AG}$ transgenic retinoblastoma mice were divided into 6 groups and received periocular injections in the right eyes of (a) saline, (b) carboplatin (31.25μg/20μl, subtherapeutic dose), (c) 2-DG (250mg/kg), (d) 2-DG (500mg/kg), (e) 2-DG (250mg/kg) + carboplatin (31.25μg/20μl) or (f) 2-DG (500mg/kg) + carboplatin (31.25μg/20μl). Mice received 60mg/kg of pimonidazole (10mg/ml) via intra-peritoneal injection two hours before enucleation. Eyes were enucleated at 20 weeks of age, snap frozen and analyzed for hypoxic regions and tumor volume.

Results
When 2-DG was combined with carboplatin, a marked decrease in tumor burden was observed that was significantly more pronounced than when either agent was given alone ($P<0.05$). Highest dose 2-DG (500mg/kg) + carboplatin decreased tumor burden by 65% ($P<0.01$) in comparison with saline controls, and by 32% compared to carboplatin alone ($P<0.05$).

Conclusion
Periocular delivery of glycolytic inhibitors as adjuvants to chemotherapy has the potential to significantly increase the efficacy of chemotherapy in advanced retinoblastoma. Localized delivery of these drugs is important in minimizing systemic toxicities and maximizing the effectiveness of therapy. This approach may have benefits for children with retinoblastoma.

Subconjunctival nanoparticle carboplatin in the treatment of murine retinoblastoma

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Background
We evaluated the efficacy subconjunctival nanoparticle carboplatin in the treatment of transgenic murine retinoblastoma.

Methods
Dendrimeric nanoparticles loaded with carboplatin were prepared. Forty LHβ-Tag mice were randomly assigned into 4 groups, and treated at 10 weeks of age. Each mouse received a single subconjunctival injection in one eye, and the opposite eye was left untreated as a control. Group 1 (high-dose nanoparticle) received 37.5 mg/ml nanoparticle carboplatin; Group 2 (low-dose nanoparticle) received 10mg/ml nanoparticle carboplatin; Group 3 (conventional carboplatin) received 10mg/ml of carboplatin in aqueous solution, and Group 4 (phosphate-buffered saline; PBS) received PBS. Mice were euthanized on day 22 after treatment. Eyes were serially sectioned, and retinal tumor burden was quantified by histopathologic analysis.

Results
Mean tumor burden in the treated eyes was significantly smaller compared to the untreated eyes in the same mice in both nanoparticle carboplatin groups (Group 1, $P=0.02$; Group 2, $P=0.02$), to the treated eyes in conventional carboplatin group (Group 1 vs. 3, $P<0.01$; Group 2 vs. 3, $P=0.01$), and PBS group (Group 1 vs. 4, $P<0.01$; Group 2 vs. 4, $P=0.01$). The untreated eyes in high-dose nanoparticle carboplatin showed significantly smaller tumor mass compared to conventional carboplatin ($P=0.03$) and PBS group ($P=0.04$). No toxicity was observed in any of the groups.

Conclusion
A single injection of subconjunctival nanoparticle carboplatin was effective in the treatment of transgenic murine retinoblastoma with no associated toxicity. The higher dose of subconjunctival nanoparticle carboplatin decreased the tumor burden in the contralateral eye.

Friday
11th September 2009

Retinal tumours

Session 2

Retinoblastoma

Periocular carboplatin for retinoblastoma: toxicity and response with 101 injections

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Background
Periocular chemotherapy has been used as an adjunct to traditional intravenous chemotherapy in an attempt to increase therapeutic intraocular levels and minimize the systemic dose.

Methods
101 periocular injections of carboplatin in 34 eyes of 29 patients were administered to advanced cases of retinoblastoma. Patient's history, demographics, dose, response, and side effect profile were reviewed retrospectively.

Results
Reason for use of periocular carboplatin included tumor recurrence in 2/34, persistent or recurrent vitreous or sub retinal seeds in 29/34, and advanced ocular disease in 3/34 patients. The median number of injections was 2 doses/eye with a range of 1 to 11. Peri-ocular carboplatin injections were used in conjunction with other chemotherapy or radiation in 29 of the 34 eyes. In the 5 eyes that periocular carboplatin was used alone complete response occurred in 1 eye, partial response in 3 eyes and no response occurred in 2 eyes. Overall 13 of the 34 eyes were saved. Orbital swelling occurred in 14 of 34 eyes and one eye had notable orbital fat atrophy. One severe reaction resulted in loss of vision to light perception that failed to recover.

Conclusion
Periocular carboplatin injections offer an additional route for delivering chemotherapy to the eye. Complications from periocular chemotherapy injection were minimal in the majority of cases. However, serious toxicity was seen in one patient.

Periocular carboplatin injection in the management of retinoblastoma with diffuse vitreous seeds

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Background
Chemotherapy combined with focal measures is highly successful in the management of retinoblastoma. However, about 60–80% of eyes with diffuse vitreous seeds fail chemoreduction, possibly because of "inadequate" vitreous penetration. This study was performed to evaluate the therapeutic efficacy of deep posterior subtenon carboplatin injection in eyes with intraocular retinoblastoma with diffuse vitreous seeds.

Methods
Design: Matched case-control study. *Participants*: Twenty consecutive patients with retinoblastoma with diffuse vitreous seeds who received deep posterior subtenon carboplatin injections (15mg in 1.5ml) in conjunction with high-dose systemic chemotherapy (vincristine, carboplatin and etoposide) and completed at least one year follow-up following complete regression were compared with a matched control cohort of twenty patients who received high-dose systemic chemotherapy alone. *Outcome measure*: Complete tumour and vitreous seed regression without need for external beam radiotherapy or enucleation.

Results
At a mean follow-up of 15 months (range 12–24 months), 16 (80%) (95% CI, 58% to 92%) had regression of vitreous seeds and 4 (20%) needed enucleation in the study group, while 3 (15%) (95% CI, 5% to 36%) had regression of vitreous seeds and 17 (85%) required external beam radiotherapy or enucleation in the control group ($p<0.001$). The absolute benefit increase by adjuvant periocular carboplatin was 65% (95% CI, 42% to 89%). The number needed to treat to prevent one enucleation was 2 (95% CI 1 to 2). Transient periocular inflammation was the only major complication.

Conclusion
Periocular carboplatin has potential beneficial role with minimal side effects in intraocular retinoblastoma with diffuse vitreous seeds.

Periocular carboplatin for retinoblastoma – with or without systemic chemotherapy?

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Background
Subtenon carboplatin injections have been shown to be effective in treating resistant retinoblastoma. We report our experience of periocular carboplatin administered in 2 settings – concurrently with systemic chemotherapy, and for residual disease after completion of systemic chemotherapy

Methods
Eleven eyes (1 unilateral, 10 remaining eye of bilateral cases) of 11 subjects treated with periocular carboplatin were included. 20mg in 2ml carboplatin was used, and number of injections ranged from 1 to 5 (mean 2.1). In 8 subjects with active vitreous disease after completion of 4 cycles of CEV chemotherapy, subtenon carboplatin was added to the remaining cycles of systemic chemotherapy. The remaining 3 subjects had completed primary chemo and local therapy (laser/cryotherapy/plaque), and subtenon carboplatin was added subsequently.

Results
Disease regression was seen after 2 injections, and continued for at least 3 months after the last injection. One eye did not need any additional treatment while 6 eyes needed additional treatment with second line chemotherapy, plaque, radiotherapy and intra-arterial chemotherapy. Three eyes subsequently underwent enucleation. A greater treatment effect was seen when periocular carboplatin was administered concurrently with systemic chemotherapy. Complications included optic nerve damage, severe conjunctival necrosis, orbital fat atrophy and enophthalmos, and motility disturbances. Any coexistent retinal tumours did not respond well to treatment, and needed additional local treatment.

Conclusion
Subtenon carboplatin is more effective against vitreous disease than retinal tumours. Treatment is more effective if given concurrently with systemic chemotherapy. There are however significant risks including total loss of vision, and these risks are magnified if open cryotherapy is applied at the same time.

Intravitreal methotrexate monotherapy as salvage treatment for recurrent retinoblastoma after standard chemoreduction

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Purpose
To document response of small retinal, subretinal and vitreal retinoblastomas (RB) to intravitreal methotrexate (MTX).

Methods
An interventional case series. In 2007–2009 three children with progressive recurrent RB developing during or after chemoreduction with vincristine, etoposide and carboplatin (VEC) for bilateral RB received 0.1ml intravitreal injections of 4mg/ml MTX in one eye to avoid high dose systemic chemotherapy or external beam radiotherapy. The protocol was modified from that used for intraocular lymphoma and consisted of induction (8 injections weekly), consolidation (4 injections biweekly) and maintenance (8 injections monthly) phases. Each injection was preceded by aspiration of 0.12ml of aqueous. A surgical sponge was used to wipe the needle when it was retracted.

Results
The first child developed a vitreous recurrence after VEC and brachytherapy. Complete response (CR), observed after induction, is maintained 9 months after end of maintenance phase. The second child developed subretinal satellites after VEC. CR, obtained after induction, persists during maintenance. A small paramacular RB in the third child progressed in spite of VEC, thermotherapy and chemothermotherapy. Partial response (PR) was obtained after induction and regression continues during consolidation. Minor conjunctival bleeding occurred after a quarter of injections. Retrograde flow through needle track was not observed. No tumor relapsed in the treated eye, whereas all children developed relapses in the fellow eye.

Conclusion
Intravitreal chemotherapy for RB is a controversial treatment for fear of extraocular spread. With appropriate precautions, single agent methotrexate can induce regression of small retinal, subretinal and vitreal tumour relapses.

Our recent modifications of local chemotherapies for preservation of eyes with retinoblastoma

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Background
We pioneered local chemotherapies for eye-preservation therapy of retinoblastoma. They consist of 3 procedures, selective ophthalmic arterial injection (SOAI) of melphalan, vitreous injection of melphalan (VIM) and vitreous surgery (VS) using irrigation of melphalan. Our more than 20 years experience and excellent suggestions or advice from abroad have made us change several parts of our original methods to improve the success rate of eye preservation.

Methods
Concerning SOAI, the dose of melphalan was increased according to Prof. Abramson's paper. It is now 5 or 7.5mg instead of 5 or 7.5mg per square metre of surface area of the patient. However, our SOAI is still using a balloon catheter. The dose of VIM was increased from 8 to 20μg/0.1ml according to the suggestion of Prof. Munier. VS with irrigation of melphalan was changed to irrigation of topotecan, considering the resistance of recurrent retinoblastoma cells after local therapies with melphalan.

Results
After these modifications, favorable success rates were achieved.

Conclusion
We recommend these 3 modifications to those who are going to try these local chemotherapies in the future.

Success or failure of intra-arterial chemotherapy for retinoblastoma: impact of orbital vascular anatomy

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Background
Although systemic chemotherapy is widely employed for the treatment of intraocular retinoblastoma its many side effects have lead us to develop a technique of ophthalmic artery canulation and infusion of chemotherapy in high concentrations but low doses. Most patients with retinoblastoma treated with intra-arterial chemotherapy are cured with this technique; we have identified structural variations and flow patterns (identifiable on arteriograms) that predict failure. Careful evaluation of the angiograms showed anatomic variations that explained the clinical findings. We describe the anatomic variations in anatomy and flow of the ophthalmic artery and their impact on success of intrarterial chemotherapy for retinoblastoma.

Methods
Arteriograms from 50 eyes that received intra-arterial chemotherapy over a two-year period were evaluated.

Results
Size of the ophthalmic artery (age of patient), anatomic variants of the ophthalmic artery and blood flow volume of normal vessels all influence the success of intrarterial chemotherapy.

Conclusion
Variations in orbital vascular anatomy and flow patterns determine the response of retinoblastoma to intra-arterial chemotherapy.

Ophthalmic arterial injection therapy for retinoblastoma patients by using melphalan: technique and eye preservation rates

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Background
Melphalan had the greatest effect on retinoblastoma in clonogenic assay. To reduce the side effects of melphalan and to acquire better response, we developed the system of selective ophthalmic arterial infusion therapy (SOAI).

Methods
All procedures were performed under general anesthesia. 4Fr introducer catheter attached with micro-balloon was used. During the temporary occlusion of ICA at the portion just distal to the orifice of ophthalmic artery, melphalan was infused form the introducer catheter. Between 1989 and 2007, 1083 SOAIs by using melphalan were planed, and 15 technical failures occurred. Technical success rate was 98.6%. Finally, 287 patients were successfully treated by SOAI (male 157, female 130, bilateral 169, unilateral 118). Most of SOAIs were performed combined with thermotherapy (microwave and/or laser), vitreous injection, or cryotherapy.

Results
Two cases of delayed ophthalmic artery occlusion were observed in patients who had multiple SOAIs. The rates of eye preservation were Ia 81.3% (13/16), Ib 88.0% (22/25), IIa 83.3% (30/36), IIb 80.8% (21/26), IIIa 74.3% (26/35), IIIb 72.3% (8/11), IVa 75.0% (15/20), IVb 80% (16/20), Va 44.8% (30/67), Vb 59.2% (61/103), in Reese-Ellsworth classification.

Conclusion
SOAI by using balloon technique is safe, will avoid the side effects of systemic chemotherapy, and may replace some parts of standard systemic chemotherapy in many countries.

Ocular and systemic prognosis of selective ophthalmic arterial injection for intraocular retinoblastoma

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Background
Selective ophthalmic arterial injection with balloon catheter was introduced in 1987, first as a salvage local chemotherapy for relapsed intraocular retinoblastoma after external beam radiotherapy (EBRT). To clarify the effectiveness and toxicities of this method we analyzed the long-time ocular prognosis, visual acuity, and systemic side-effects.

Methods
A retrospective review of patients with retinoblastoma treated with selective ophthalmic arterial injection from 1987 to 2007.

Results
1470 injections were performed for 408 eyes of 343 patients. Melphalan was injected at the dosage of 5-20mg/m^2 body surface. The technical success rate was 98.8%. Severe side effects were orbital apex syndrome (2 cases, 0.5%) and diffuse chorio-retinal atrophy (2 cases, 0.5%). Transient periocular swelling and vomiting occurred in some cases, but no other systemic side effect including neutropenia was experienced as expected. Secondary neoplasm occurred in 11 cases who received EBRT. Fifty per cent of group D and 35% of group E eyes were preserved. More than half of eyes without macular tumor keep visual acuity better than 20/30, independent of total melphalan dose. Some eyes were treated with arterial injection as an initial treatment, and 60% of group B eyes were preserved without radiotherapy and systemic chemotherapy.

Conclusion
Selective ophthalmic arterial injection with balloon catheter was effective and has few severe side-effects in the short and long term. Good visual function can be expected.

Direct intra-arterial (ophthalmic artery) chemotherapy with melphalan for advanced intraocular retinoblastoma: the Italian experience

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Objective
To report the preliminary results of the conservative treatment of advanced retinoblastoma (Staging Va and Vb) obtained with the melphalan protocol (direct intra-arterial-ophthalmic artery infusion of melphalan)

Materials
13 children with advanced retinoblastoma eyes who were eligible for enucleation were entered in phase two of one center open study-approved protocol of ophthalmic artery infusion of melphalan to avoid enucleation (Italian melphalan protocol, approved by the Ethic Committee, Hospital of Siena). Ten of them have been successfully treated; in three of them it has not been possible to conclude the procedure due to haemodynamic problems.

Methods
Cannulation of the ophthalmic artery was performed by a femoral artery approach using microcatheters (magic 1.5) while the children were under general anesthesia and anticoagulated. Chemotherapy (melphalan) was infused into the artery over a 30-minute period (dose of 3–5mg of melphalan according to the age and size of the globe). Local and systemic toxicity has been evaluated and documented.

Results
The ophthalmic artery was successfully cannulated in 13 cases (total: 35 procedures). In 3 attempts was impossible to successfully conclude the procedure due to haemodynamic problems. Dramatic regression of relapse was seen in 8 cases, and of tumor, vitreous seeds, and subretinal seeds in two cases. No severe systemic side effects (sepsis, anemia, neutropenia, fever, or death) occurred. No transfusions were required (red cells or platelets). Nine patients developed lid rush which resolved without treatment in a few days. There was no toxicity to the anterior segment. In five patients unilateral ptosis has been observed. Follow-up range is 1–9 months.

Conclusion
13 children with advanced retinoblastoma (Stage Va and Vb Reese classification) were eligible for the melphalan Italian protocol. Ten children have been successfully treated with the intra-arteriously given melphalan technique. Seven cases were relapses after systemic chemotherapy, two cases were relapses following chemo and radiotherapy; only one case has been treated directly with melphalan at diagnosis.

ERG monitoring of retinal function after intra-arterial chemotherapy infusion for retinoblastoma

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Background
Beginning in May 2006, patients with advanced retinoblastoma (Stage V) have been offered intra-arterial chemotherapy infusion treatment at our institution as an alternative to enucleation, under an IRB-approved protocol, which includes ERG monitoring of retinal function. This report summarizes our experience.

Methods
ERG recordings are obtained during routinely-scheduled examinations under anesthesia using a modified ISCEV-standard protocol (to minimize the duration of general anesthesia) using a hand-held mini-ganzfeld flash stimulator. Photopic recordings are obtained to single flash and 30-Hz flicker stimuli; the patient then dark-adapts for 5 minutes, and scotopic responses to a rod-isolating dim flash, matched red flash, and full-strength ISCEV standard flash are recorded.

Results
Of 55 patients enrolled (intent-to-treat), ERG data (237 studies) are available for 51 eyes of 47 patients. Responses prior to treatment range from excellent, even in eyes with very large tumors, to extinguished, in eyes with total retinal detachment. Responses are recordable during and after intra-arterial chemotherapy in 2/3 of cases, and may improve, especially in eyes where tumor regression is accompanied by retinal reattachment. Reductions in ERG are seen in eyes which progress to retinal detachment, and in eyes with severe vasculopathy following radiation treatment.

Conclusion
ERG monitoring following intra-arterial chemotherapy for retinoblastoma suggests the treatment is well-tolerated in most treated eyes, with preservation of retinal function and at least some visual potential in 2/3 of cases. ERGs are reduced in eyes with retinal detachment and radiation retinopathy.

The histopathological evaluation of retinal toxicity in retinoblastoma eye treated by ophthalmic arterial infusion of melphalan

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Background
As a treatment method for retinoblastoma, ophthalmic arterial infusion of melphalan solution (OAIM) is useful. However, the retinal toxicity of OAIM is not yet well known. We conducted a pathological investigation of whether there is any correlation between repeated times of OAIM and retinal toxicity.

Methods
The subjects comprised five retinoblastoma eyes from five cases those were treated by ocular preservation therapy followed by enucleation at the National Cancer Center Hospital between 2005 and 2008. In these cases, VEC systemic chemotherapy was first performed, and thereafter once to six times OAIM were carried out. In some cases, either TTT or cryotherapy was used concurrently. Subsequently, when the tumor invaded the optic nerve head, the eye was enucleated without external beam radiotherapy. We made histopathological examination of the enucleated eye and evaluated the retinas that were not affected by either TTT or cryotherapy and seemed to be generally normal.

Results
The retinal layer structure was maintained. However, in comparison to retinoblastoma eye enucleated without ocular preservation therapy, each layer of the retina, especially the inner nuclear layer and outer nuclear layer, had become thinner. The degree of retinal thinning was not correlated to repeated times of OAIM.

Conclusion
We could not find any correlation between repeated times of OAIM and retinal toxicity. Repeated application of OAIM does not seem to bring harmful effects on the retina.

Systemic (non-ocular) toxicity associated with intra-arterial melphalan chemotherapy: the New York experience

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Background
Intra-arterial chemotherapy is a promising strategy for intra-ocular retinoblastoma, but only limited data exist regarding the non-ocular systemic toxicity associated with the treatment.

Methods
143 cycles of melphalan-containing intra-arterial chemotherapy have been administered to 48 patients as of April 6 2009. Families were asked to obtain a complete blood count 7 to 10 days post-treatment. 79 cycles administered to 38 patients were evaluable. Cycles were considered to be inevaluable if (1) blood count results were not available in the 7 to 14 days post-treatment interval or (2) concurrent intravenous chemotherapy was administered. Toxicity was assessed via the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.

Results
13 (16%) cycles administered to 10 (26%) patients were associated with grade 3 (n=10) or grade 4 (n=3) neutropenia. One patient was admitted for one night due to uncomplicated fever and neutropenia. No patient suffered ≥ grade 3 RBC or platelet toxicity or received a blood product transfusion. No ≥ grade 3 non-hematopoietic non-ocular toxicity was encountered. No case of stroke has occurred.

Conclusion
Intra-arterial melphalan-based chemotherapy is generally well-tolerated. Neutropenia is the only significant systemic non-ocular toxicity that has been encountered.

Evaluation of the radiation exposure of angiography for intra-arterial chemotherapy administration for retinoblastoma

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Background
Intra-ophthalmic artery chemotherapy administered 3–4 times using cerebral angiography (CA) is being used for children with retinoblastoma (RB). In this review, we estimate cumulative radiation dose during angiography delivered to the orbital bone, brain, lens, and thyroid and the associated risks.

Methods
A literature review was performed to evaluate doses to the skin surface, brain, lens and thyroid during cerebral angiography.

Results
Typical fluoroscopy times for a pediatric patient undergoing CA are 10–12 min, with a skin dose rate of 4–6 mGy/min. During digital subtraction angiography (DSA), typically 250 and 40 frames are taken from the frontal and lateral views, respectively, with a 0.6–0.9 mGy/frame surface dose. Median surface doses are 40–60 mGy for fluoroscopy and 220–260 mGy for DSA. The bone receives 80–85% of the surface dose in child younger than 2y. The dose is 50% and 20% at 3cm and 5cm into the brain. The eye and lens likely receive full dose; the thyroid receives 2–3% of the dose. Cumulative doses to the skin, bone, brain, eye, lens and thyroid after 3 procedures can be 150 mGy, 120 mGy, 75 mGy, 150 mGy, 150 mGy, 5 mGy, respectively, and may be five fold with DSA. Doses in this range may increase the absolute risk of a fatal cancer by up to 1%, and probably higher in RB patients.

Conclusion
The use of CA should be monitored carefully and a concerted effort should be made to use optimal techniques which minimize dose radiation dose to these children.

Enucleation after treatment with intra-arterial chemotherapy for retinoblastoma: a report on 10 cases

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Background
Although intra-arterial chemotherapy (IAC) has been performed over 1,000 times (greater than 900 times in Japan and greater than 150 times in New York), very little pathologic information is available for the eyes enucleated after treatment. We now have three years of experience with super-selective ophthalmic artery infusion of chemotherapy. Here we report the pathologic findings of IAC treated eyes that were subsequently enucleated.

Methods
Independent pathologic review of the enucleated eyes was correlated with the clinical findings that prompted enucleation.

Results
Of 55 eyes receiving IAC, 10 had been enucleated by the end of April 2009. 6 were Reese Ellsworth Group 5B, 2 were Group 5A, and 2 were 3A. Of the 21 eyes that were treated with IAC as the primary treatment, one was enucleated; its pathology revealed residual non-necrotic, non-calcified tumor. Of the 34 eyes treated with IAC after other treatments, 9 were enucleated. 3 of these had persistent, non-calcified, non-necrotic tumor. Kaplan-Meier analysis of probability of maintaining the eye at 3 years was 88% in the group treated with IAC as the primary treatment, 65% in those receiving IAC as salvage treatment, and 71% overall. All patients are alive and free of metastatic disease.

Conclusion
Of the patients who had IAC as their primary treatment, fewer than 5% of the eyes were enucleated. Of the patients who had failed other treatments, 26% were enucleated. Of the enucleated eyes, 4 had persistent non-calcified, non-necrotic tumor on pathology.

Uncovering the mechanism of action of cardenolides as novel therapeutic agents for retinoblastoma

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Background
Intrarterial chemotherapy constitutes an exciting approach for the treatment of advanced intraocular retinoblastoma. We have previously identified cardenolides as a well-known class of cardiotonic drugs that could be repositioned for treating retinoblastoma if administered locally via direct intrarterial infusion. While the Na+/K+ ATPase is generally thought to be responsible for the antitumor effects of cardenolides, our goal is to understand the mechanism of action of cardenolides in retinoblastoma cells.

Methods
Our approach consists in employing RNAi technology in combination with cardenolide treatment to identify the molecular pathways implicated in the cellular response to cardenolides in retinoblastoma cells. The use of a multiplexed readout allows us to identify genes whose knockdown of expression modulates the antiproliferative effect as well as the induction of apoptosis caused by cardenolides.

Results
Our study probes the implication of the Na+/K+ ATPase in the response to cardenolides. In addition, we investigate whether the specific knockdown of expression of p53 and MDM2 can modulate the effect of cardenolides in retinoblastoma cells.

Conclusion
Our results provide important clues for the elucidation of the mechanism of action of cardenolides in retinoblastoma cells and pave the way to the first genome-wide RNAi screen in retinoblastoma cells. We expect that our work could lead to the identification of potent combination therapies for the treatment of retinoblastoma by intrarterial delivery of cardenolides.

Friday
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Retinal tumours

Session 3

Retinoblastoma

Carboplatin induced ototoxicity in retinoblastoma patients treated with systemic chemotherapy

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Purpose
Platinum induced ototoxicity manifests as a bilateral high-frequency sensorineural hearing loss. Incidence and severity increase with cumulative dose. Carboplatin, although considerably less ototoxic than cisplatin, has been linked to sensorineural hearing loss. We retrospectively studied the cumulative incidence (CI) of ototoxicity in patients with intraocular retinoblastoma treated with systemic carboplatin.

Methods
Baseline and serial audiology exams were retrospectively reviewed. Exams were graded using the National Cancer Institute's, Brock's and Children's Cancer Group criteria. Toxicity was graded 0 to 4, with 0 being normal and each successive number indicating greater toxicity. An abnormal study was defined as a value greater than 0 using any of the three grading schemes.

Results
We identified 61 patients (35 males, 49 bilaterals) with a median age of 9 months at diagnosis treated with systemic carboplatin for intraocular retinoblastoma. Carboplatin dosing was based on body surface area (n=42), the Calvert Formula (n=6), or a combination of the two methods (n=13). The median number of audiology exams per patient was 4. Twelve patients (10 bilaterals) experienced an abnormal hearing test within a median time of 1.22 years. The CI of any degree of ototoxicity was 21.7%. Patients less that 6 months of age at diagnosis had a significantly greater CI of hearing loss than older patients (33.89% vs 11.94%, p=.0059).

Conclusion
Carboplatin induced otoxicity is a significant risk in retinoblastoma patients, greatest in those diagnosed before 6 months of age. Auditory screening is needed both during and after exposure to systemic carboplatin.

Pineal gland changes in patients with retinoblastoma treated with systemic chemotherapy

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Background
The incidence of trilateral retinoblastoma has been reported to decrease in the era of chemoreduction. One possible explanation is the prophylactic treatment of pineal tumors. We therefore studied the size of the pineal gland over time in patients with hereditary retinoblastoma treated with systemic chemotherapy.

Methods
Transverse and longitudinal measurements of the pineal gland were taken from magnetic resonance (MR) images and plotted over time. Findings were correlated with both pineal cysts and formation of new ocular tumors after beginning chemotherapy.

Results
Of 51 consecutive patients with hereditary retinoblastoma treated with systemic chemotherapy, 37 (21 males, 35 bilateral) had transverse and longitudinal measurements of the pineal gland from diagnosis (median age 4.5 months). Pineal cysts were seen in 4 patients at diagnosis; 11 patients later developed cysts. Patients with cystic changes had significantly larger pineal glands ($p<.0001$), but there was no significant difference in change in size over time. In contrast, the pineal glands of the 7 patients that developed new ocular tumors demonstrated a significant change in size over time ($p=.0073$) but were not significantly larger. Median follow-up was 2.7 years.

Conclusion
Pineal cysts are common MR findings in hereditary retinoblastoma patients, but do not predict a greater rate of growth. However, new ocular tumor formation after chemotherapy begins does predict a significantly greater rate of growth of the pineal gland. Such patients warrant close surveillance with serial MR imaging of the pineal gland, as the impact of systemic chemotherapy on preventing the formation of pinealoblastoma remains unknown.

A multi-center model for the management of retinoblastoma: a virtual RB center

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Purpose
To describe a multi-center, multi-institutional model for the clinical management and research of retinoblastoma.

Method
Single center observational report.

Findings
Combining the clinical and research faculty of four local institutions, The Retinoblastoma Center of Houston represents a virtual citywide RB program. By providing multiple-site patient care, the resources of the region's best cancer and children's hospitals, ophthalmic clinical and pathology programs can be accessed for the multi-specialized care critical for retinoblastoma. These combined resources enable the center to contribute significantly to cooperative group protocols, phase I/II drug development, gene transfer, radiation oncology and translational research. Combined databases and tumor boards form the basis for shared clinical and research endeavors.

Conclusion
Creation of a virtual city wide retinoblastoma program is a unique model for RB patient care and research whereby multiple sites consolidate their expertise in the management of retinoblastoma.

Ocular outcomes after external beam radiotherapy as second line conservative management of retinoblastoma

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Background
Conservative management of intraocular retinoblastoma currently requires a combination of several treatment modalities, often comprising systemic chemotherapy and laser thermotherapy. The aim is to avoid first line external beam radiotherapy (EBR) and its well known side effects, in particular the increased risk of secondary tumor in the irradiation field. Nevertheless EBR may be the last conservative salvage treatment attempt in case of failure of the initial treatment.

Patients and methods
Retrospective study of children treated in our institution by EBR as a second line conservative management of retinoblastoma from 1995–2005.

Results
During the study period 38 children (41 eyes) required salvage EBR, 8 children are lost to follow-up and analysis is realized on 30 children (33 eyes). The median follow-up is 50 months. Secondary enucleation was necessary in 60% of the eyes (75% of them were enucleated for persistent tumor activity). Visual acuity in the retained eyes was available for 12 children (12 eyes). VA was >20/200 in five cases, 20/200 or less for seven.

Conclusion
EBR remains an option in case of relapse after current first line conservative treatment, including chemotherapy. Nevertheless the indication of such a second line treatment must be evaluated, taking into account the poor results regarding ocular preservation and vision, as well as the potential risks of second tumors.

Histopathology of retinoblastoma after primary chemotherapy

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Objective
Histopathologic evaluation of eyes enucleated after neoadjuvant chemotherapy for retinoblastoma.

Methods
Retrospective case series, including 52 eyes (51 patients) of retinoblastoma, enucleated after primary chemotherapy. Clinical data was collected by medical records review regarding clinical presentation, chemotherapy regimen, number of cycles, response to chemotherapy, and indications for enucleation. Histopathological slide review was performed by a single experienced pathologist masked to the clinical data.

Main outcome measures were presence of viable tumor cells, their location and differentiation, secondary changes, mitotic figure counts and presence of histopathologic risk factors.

Results
Twenty-two eyes had initially presented with proptosis. Twenty eyes (38.4%) were clinically phthisical after chemotherapy. Viable tumor cells were present in 29/52 (55.7%) of the eyes post chemotherapy, and in 7/20 eyes (35%) which appeared phthisical. Histopathological risk factors were present in 15/52 (28.8%) of the eyes. Among the viable tumor cells, 34.4% (10/29) were poorly differentiated tumors, 13.7% (4/29) well differentiated, 31% (9/29) retinocytoma-like areas and 20.9% (6/29) were mixed populations. 20% of the phthisical eyes harboured undifferentiated cells. Six patients were lost to follow up after enucleation. Five patients (10.8%) developed metastasis, 3 to brain and 2 to bone marrow. Three of these showed viable cells on histopathological assessment. One patient who was lost for follow-up was reported dead of unknown cause.

Conclusion
Evaluation of enucleated retinoblastoma eyes for residual risk factors and appropriate management is important even in clinically phthisical eyes post chemotherapy.

Retinoblastoma (Rb) in older children: a clinicopathological profile

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Background
Retinoblastoma remains the commonest primary intraocular malignancy of childhood worldwide with ~90% diagnosed at <5y age, and incidence declining as age advances.

Objective
To determine the clinicopathological profile of retinoblastoma especially in children of 5 years and above.

Methods
Retrospective review of all children aged 5 years and above was undertaken, presenting to our Ocular Oncology Clinic [and diagnosed of retinoblastoma on histopathology] between Jan 2005 – March 09 at our tertiary eye care centre.

Results
A total of 44 such older children [27M:17F] were noted (age range 5–14y, mean 6.3y ±1.7), 39/44 being unilateral. The median age of presentation was 7y, and mean duration of symptoms 6m. Leucocoria (19) was the commonest presenting symptom, 13 patients presented with painful eyes, 4 with squint, 2 with sudden visual loss because of associated hemorrhage, 5 with proptosis and 1 with a pre-phthisical eye. Anterior segment involvement with glaucoma was seen in 15 cases. Optic nerve involvement and metastases were noted in few patients. According to the International Classification of Retinoblastoma, 38 cases were classified into Group E and underwent primary enucleation for the worse eye. On their histopathology, majority revealed poorly differentiated Rb tumour cells.

Conclusion
Because of its lower incidence and varied presentation in older children, the diagnosis of retinoblastoma can often be delayed in such eyes leading to advanced disease at the time of presentation. Awareness of the same on the part of both the clinician and the parents is imperative.

Lack of correlation between the histology and magnetic resonance imaging of the optic nerve in eyes primarily enucleated for retinoblastoma

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Background
The ability of magnetic resonance imaging (MRI) to distinguish between pre-laminar and post-laminar optic nerve invasion is debated. We, therefore, undertook a retrospective clinicopathologic study to correlate the histology and the MRI of the optic nerve in eyes primarily enucleated for retinoblastoma.

Methods
The histopathology of 67 eyes from 67 patients with retinoblastoma who underwent primary enucleation between March 1997 and January 2008 was studied for optic nerve invasion. Two examiners independently reviewed pre-operative gadolinium-enhanced T1 weighted magnetic resonance images. A weighted kappa statistic was used to assess agreement between observers. The MRI interpretations were correlated with the histological findings.

Results
Of the 67 eyes studied, 59 had preoperative MRIs available for review. Moderate agreement existed between radiologists (kappa value 0.55). Poor and fair agreement existed between the two radiologists and pathologist (kappa values 0.29 and 0.17). Exophytic tumors showed the greatest disparity (kappa value -0.125) between MRI and pathology.

Conclusion
We found limited correlation between MRI and pathology in assessing optic nerve invasion in eyes with retinoblastoma. Magnetic resonance imaging, although useful in the evaluation of retinoblastoma, has limited utility in assessing the exact extent of optic nerve invasion; high-risk features of retinoblastoma such as post-laminar invasion remain best defined by pathology. Enucleating surgeons should still attempt to resect the longest, safest length of optic nerve possible. Pediatric oncologists should be judicious in prescribing neoadjuvant chemotherapy based on MRI findings.

High-risk features and tumor differentiation in retinoblastoma: a retrospective histopathologic study

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Context
Histopathologic risk factors are important indications for adjuvant chemotherapy in patients with retinoblastoma.

Methods
387 eyes with retinoblastoma treated by enucleation at an American eye hospital between 1986 and 2008 were examined retrospectively to assess the frequency of histopathologic risk factors. The relationship between tumor differentiation and age, and the frequency of photoreceptor differentiation and the role of retinoma/retinocytoma as a retinoblastoma precursor also were examined.

Results
55 of 297 (18.5%) previously untreated eyes had high-risk features. Retrolaminar optic nerve invasion was present in 10.4% and 8.1% had massive uveal invasion. There was a statistically significant inverse relationship between age at enucleation and tumor differentiation characterized by the number of rosettes. 20.4% of all tumors contained foci of photoreceptor differentiation (PRD), which were localized in the base of a predominantly endophytic tumor in about one fourth. Lack of correlation between PRD and age at enucleation suggests that malignant transformation occurs quite early or prenatally. Both preceding observations provide evidence for the hypothetical role of retinoma as a retinoblastoma precursor.

Conclusion
High-risk histopathologic features that currently are indications for adjuvant chemotherapy were found in slightly less than one in five infants with retinoblastoma enucleated at a large American eye hospital. Retinoblastomas become progressively less differentiated with time, and may be spawned by precursor retinomas.

Risk of second cancers following treatment for retinoblastoma since 1970

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Background
Children with hereditary retinoblastoma survive into adulthood, but are at increased risk of second cancers due to genetic predisposition, enhanced by radiotherapy. To evaluate whether children treated since 1970, when radiotherapy doses decreased and chemotherapy use increased, are at risk of developing second cancers, we analyzed cancer risk in a large retinoblastoma cohort.

Methods
Retrospective cohort of 867 survivors treated 1970–1996 in New York and Boston. The observed number of second cancers was compared to the expected based on general population rates (standardized incidence ratio [SIR]). We estimated the relative risk (RR) of second cancers associated with sex, age at retinoblastoma, attained age, hereditary status and treatment.

Results
Since 1970, 56 second cancers were diagnosed in 476 hereditary (SIR=30, 95%CI 23–39), and two cancers in 391 non-hereditary patients. The highest risks occurred 10-19 years after retinoblastoma (SIR=51, 95%CI 34–74) for cancers arising in the radiation field. Risks for second cancers were associated with hereditary versus non-hereditary disease (RR=18, p=0.001); any radiation versus no radiation (RR=12, p=0.001); and any chemotherapy versus no chemotherapy (RR=1.7, p=0.07). We noted a 40% lower risk of second cancers in hereditary patients irradiated >12 months of age. Patients treated after 1970 experienced a non-significant 20% lower relative risk of second cancers compared with those treated earlier.

Conclusion
Hereditary status and radiotherapy remain major determinants of second cancers. Retinoblastoma patients treated in the past few decades appear to have a lower risk of second cancers, but more follow up will be needed to confirm this trend.

Uterine leiomyosarcoma in retinoblastoma: risky enough for prophylactic intervention?

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Background
We have previously reported a substantial excess risk for leiomyosarcomas (LMS) of the corpus uteri more than 30 years after diagnosis of hereditary retinoblastoma. Here, we describe the patient and risk characteristics for uterine LMS and discuss options for early detection and appropriateness of prophylactic actions.

Methods
A cohort study and retrospective chart review. The excess risk was calculated as the observed number of uterine leiomyosarcoma minus the expected number based on general population rates times 10,000.

Results
In our cohort of 900 female retinoblastoma survivors, 5 of 525 hereditary retinoblastoma patients developed uterine LMS, resulting in an excess risk of 3.87. Only one uterine LMS was diagnosed in 375 non-hereditary survivors. Among hereditary patients who developed uterine LMS the excess risk increased dramatically: to 20 for female hereditary retinoblastoma patients aged between 30–39 years, and to 27 for patients aged 40+ years. Radiotherapy for retinoblastoma did not confer a higher excess risk for uterine LMS. The average age of uterine leiomyosarcoma diagnosis was at 39.2 years.

Conclusion
There is a substantial excess risk of uterine LMS in female hereditary retinoblastoma patients, particularly over 30 years of age. As more patients survive into their thirties, this number is likely to increase. The inadequacies in screening for leiomyosarcoma, both through imaging modalities and via endometrial biopsy, make early detection of this disease very difficult. We discuss the need for collaborative enhancement of screening tools, and provide a perspective on the appropriateness of prophylactic hysterectomy.

The role of education in the promotion of red reflex assessments and the sensitivity of this test

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Background
The assessment of the red reflex by primary care physicians is essential to ensure that children with retinoblastoma and sight threatening conditions are seen as early as possible. The purpose of this study is to assess the nature and frequency of abnormal red reflex referrals before and after an educational strategy was used.

Methods
A retrospective audit was conducted from September 2005 to September 2006. Posters were sent to 200 General Practitioner (GP) practices in London and pathways for referrals given. In addition paediatricians within one hospital were sent posters. A prospective audit was conducted from October 2006 to January 2009.

Results
Prior to posters being sent, there were no referrals from primary care physicians with abnormal red reflexes. Following the posters being sent, 28 abnormal red reflex referrals were made over a period of 27 months; 24 from GPs and 4 from neonatologists. 13 were detected at 6 weeks of age (routine screening). 3 patients had a positive finding (2 with bilateral cataracts and 1 with hypermetropic astigmatism). 20 physicians responded to questioning and 11 stated that they had seen the posters. 5 were self-referrals. Sensitivity of this test was 11%.

Conclusion
Although an increase in referrals suggests that the assessment of the red reflex is being performed and public awareness has increased, the sensitivity of this test remains low. Management strategies need to be in place to deal with an influx of patients who may have normal assessments and a strategy in East London will be discussed.

Coping strategies of retinoblastoma survivors in relation to behavioural problems

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Background
To assess behavioural problems and coping strategies of long-term retinoblastoma (RB) survivors and explore predictors of behavioural functioning.

Methods
This population-based cross-sectional study included 117 RB survivors (12–35 years), registered in the Dutch national RB register. Survivors were asked to fill in coping, social support and behavioural questionnaires, and situational characteristics were obtained from medical archives and from an interview. Prevalence rates of coping strategies were computed based on self-reports. One-sample t-tests were applied to analyse differences in the use of coping strategies compared with healthy reference samples. Multiple regression analyses were performed to identify various predictors for behavioural problems within the RB sample.

Results
RB survivors differed from their healthy reference group in one coping style, i.e. they showed significantly less emotion-oriented coping behaviour. Adolescents who came from a single-parent family and/or experienced lower social support and used more emotion-oriented coping reported more total problem behaviour. More internalising problems were reported for adolescents who experienced less social support and less acceptance of the disease. For adults, more life events, emotion-oriented coping and lower social support explained more total problem behaviour, especially internalising problems.

Conclusion
Perception of behavioural problems seems to differ between age groups. RB survivors showed less emotion-oriented coping behaviour compared with the reference group. Behavioural problems are best predicted by social support, life events other than RB, acceptance of the disease and emotion-oriented coping, and not by medical variables. Therefore, coping and acceptance should be taken into consideration during interventions for this group.

Innovative tools for use with children who have undergone enucleation

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Background
Enucleation is a life-changing event for those undergoing surgery and their families. The Retinoblastoma Service in Birmingham sees approximately 10–15 children per year undergoing enucleation of one or both eyes. Whilst working with families affected by this condition, I was confronted by the lack of suitable tools available to assist these families to learn how to manage the care of the artificial eye.

Methods
The results from a postal audit contributed to the development of a unique support programme which covers the pre and post operative period using a model head with removal eyes; photo preparation booklets and a DVD illustrating how children and parents care for an artificial eye. The majority of the programme is home based with incentives and one to one appointments at a nurse led clinic. The programme is patient led and therefore the time it takes to complete the programme is variable.

Results
From January 2006 to December 2008 there were 50 enucleations. Of these 27 participated on the support programme and with another 25 children from the retinoblastoma outpatients clinic also participated. 49 of these children have successfully completed the programme. 2/3rd of the children on the programme used the model heads to learn the technique of removing and replacing an artificial eye.

Conclusion
The use of realistic model heads enabled children and parents to be confident and competent in learning how to care for a prosthesis in a safe environment and with a tool that they could relate to.

Are socioeconomic status and ethnicity risk factors for late presentation of retinoblastoma in the UK?

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Background
To identify the prevalence of advanced retinoblastoma (International Intraocular Retinoblastoma Classification Group E) in patients presenting to a UK retinoblastoma centre, and to investigate the relationship between socioeconomic status, ethnicity and advanced retinoblastoma at initial presentation.

Methods
A retrospective review of paediatric ophthalmology cases presenting with advanced retinoblastoma (IIRC-group E including buphthalmos, neovascular glaucoma and periorbital swelling) between January 2006 and December 2008. Demographic parameters: age at diagnosis, gender, and ethnicity were extracted from the patients' records.

The socioeconomic status of each patient was estimated from the patient's residential postcode using the ACORN index. The ACORN indices were classified into two groups (group 1: wealthy achievers, urban prosperity, and comfortably off; group 2: moderate means and hard-pressed).

Results
During the 3-year study period, 80 patients were diagnosed with retinoblastoma. 25 (30%) aged 2 months to 5 years were of the IIRC group E (mean age 26 months). 12 were male and 13 female. Out of the 25 patients, 13 were classified as group 1 (52%), and 12 as group 2 (48%), with only 16% being from the "hard pressed" category.

Most patients were from "English/Scottish/Welsh" ethnic group (68%), the remaining 32% had equal distribution among other ethnic groups.

Conclusion
Although there are some anecdotal reports that low socio-economic status may be a risk factor for late presentation of retinoblastoma, in this observational study no particular socioeconomic status seems to be related to the presentation of advanced retinoblastoma. In addition, there is a proportionate distribution of ethnicity amongst patients.

National consensus achieved through the Canadian Retinoblastoma Care Guidelines

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Background
In a series of meetings, a multidisciplinary team of parents, survivors, healthcare providers and scientists formulated the First Canadian Guidelines to standardize a high quality of care and ensure equal access to such care for children and families with retinoblastoma.

Methods
We formulated a set of evidence-based recommendations, after considering expert opinions, and benefits and risks of interventions. We evaluated the evidence used to support recommendations, grading them according to criteria from published guidelines for other diseases. When possible, the guidelines were developed in accordance with the Canadian Medical Association Handbook on Clinical Practice Guidelines, and the criteria specified in the Appraisal of Guidelines Research and Evaluation (AGREE) Instrument.

Results
We produced a comprehensive Canadian Guidelines for Retinoblastoma Care covering geographical access to care and psychosocial resources for families and healthcare givers. When high-quality evidence was unavailable, recommendations were based on clinical experience and consensus of experts. Group members achieved unanimous consensus by study, dialogue, and cooperative revision. An International Expert Advisory Committee reviewed the Guidelines which are now submitted for publication and dissemination.

Conclusion
Achieving consensus in the first Canadian Guidelines for Retinoblastoma Care is the first step towards creating a National Retinoblastoma Strategy. We need further research and a coordinated international effort to provide high-level scientific evidence in retinoblastoma, which is not always available. The Guidelines will facilitate a uniform approach to the management of retinoblastoma in Canada, for the benefit of patients and their families. We will provide this framework to any other developed or undeveloped countries for adoption to their unique situations, in support of optimal care for children and families with retinoblastoma.

Long-term retinoblastoma follow-up: with or without general anaesthesia?

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Background
Children with treated retinoblastoma undergo frequent examinations to monitor for recurrence. Repeated examinations under anaesthesia are stressful for the family, subject the child to medical risk and consume resources but allow a more complete examination in younger children. The risk of recurrent or new tumours declines with age, and it is common practice to examine older children awake. To our knowledge there are no studies on the safety and cost effectiveness of this practice, or guidelines on when awake examinations can be safely commenced.

Method
A retrospective case note review of 114 sequential patients treated for retinoblastoma in a specialist centre over 10 years.

Results
151 eyes of 114 children were included. The mean age at diagnosis was 21 months (range birth–71 months). There were 77 unilateral and 37 bilateral cases. Awake examination was commenced at a mean age of 49 months (range 19–84 months). The age of conversion to awake examination was largely dependent on child cooperation, disease activity, tumour location, laterality and whether the affected eye was enucleated.

The mean follow up was 47 months (range 8–155 months). Recurrences were detected on awake examination in two patients 38 months and 9 months after the last treatment; at age 63 months and 86 months respectively; located at the posterior pole and mid-periphery. No new tumours developed after commencing awake examinations.

Conclusion
Timely examination without general anaesthesia does not seem to expose children to an increased risk of undetected tumour growth. We emphasise the important factors which should be considered when deciding when awake examinations can be initiated.

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Retinal tumours

Session 4

Retinoblastoma

Other retinal tumours

An unexplained mechanism for familial retinoblastoma

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Background
The predisposition to develop retinoblastoma (RB) is inherited as an autosomal dominant trait. Apparently unusual patterns of inheritance in a family can be seen in families with reduced penetrance mutations or when an individual is mosaic for a mutation. Both can cause clinically unaffected individuals to have affected children. When present, mosaicism occurs in the founder family member and the offspring of that individual inherit either the normal or abnormal gene and are not expected to be mosaics themselves.

Case study
We describe a family where we have not been able to explain the occurrence of RB in two affected family members. The adult son of an affected mother wanted to know his risk of having a child with RB. He had been routinely checked under EUA as a child and had been unaffected. His mother was found to have a high penetrance RB1 nonsense mutation (p.R579X) and this was not detected in his blood. He was reassured that his children were at population risk for RB. However, his first child was diagnosed with bilateral RB at three months and was found to carry the same mutation as her affected grandmother. There is no wider family history of RB.

Results
Paternity of the child has been confirmed. The child's mother is unrelated to the family and does not carry the RB mutation. As yet, the mutation has not been detected in blood, hair, buccal cells or sperm from the unaffected man, effectively excluding mosaicism except at a level of $<5\%$. Further testing is continuing.

Conclusion
We initially thought that this situation could be caused by revertant mosaicism in the male, i.e. that he inherited the mutation from his mother but lost the mutation early in development, leaving the majority of his cells with only the normal allele. This cannot be excluded but is an extremely unusual mechanism and is not supported by the fact that the mutation cannot be detected in a variety of tissues. The other possibility is that the male inherited the normal allele from his mother and that a new mutation occurred in this allele in the child. This is unlikely but cannot be excluded.

This situation has implications for the future management of RB families and may have implications for the information provided to families with other dominant genetic disorders.

A subset of retinoblastoma without RB1 gene mutation shows high level MYCN gene amplification

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Background
Retinoblastoma is the prototypic genetic cancer caused by loss of both alleles of the RB1 gene (M1 and M2). We have established that specific genomic changes (M3 to Mn) are required for malignant transformation to retinoblastoma, including copy number changes of the tumor suppressor CDH11 and oncogenes KIF14, MYCN, E2F3 and DEK. Using sensitive molecular techniques, we detect at least one mutant RB1 allele in 98% of primary retinoblastomas. The remaining 2% of have no detectable RB1 mutations or loss of heterozygosity. We term these tumors "$RB1^{+/+}$ retinoblastoma".

Methods
QM-PCR was used to measure copy numbers of M3-Mn genomic changes in 27 primary $RB1^{+/+}$ sporadic unilateral retinoblastomas from 4 independent centers. Array comparative genomic hybridization (aCGH) was used for whole genomic profiling of the $RB1^{+/+}$ retinoblastomas. Immunohistochemistry was used to analyze expression level and localization of full-length RB protein (pRB) and MYCN protein in two primary $RB1^{+/+}$ tumors, with and without MYCN amplification.

Results
QM-PCR revealed that $RB1^{+/+}$ retinoblastomas have fewer prototypical Mn genomic changes and a significantly higher frequency MYCN amplification (37%) than $RB1^{-/-}$ primary retinoblastomas (0%) ($P=5.90 \times 10\text{-}10$, two-tailed proportion test with Yates' continuity correction). aCGH confirms that $RB1^{+/+}$ retinoblastomas do not show the typical genomic signature. Immunohistochemistry suggests that two $RB1^{+/+}$ retinoblastoma express full-length pRB and elevated levels of MYCN protein.

Conclusion
This data challenges the understanding that all retinoblastomas are caused by RB1 mutation. We now question whether MYCN amplification can replace the need for RB1 mutations in a rare subset of non-hereditary retinoblastoma.

Apparent cancer cells not derived from the malignant clone in retinoblastoma tumors

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Purpose
This study was undertaken to test the hypothesis that cells in a solid tumor are solely derived from a malignant clone.

Methods
Although some retinoblastoma tumors express dysfunctional Rb protein, most tumors are the result of nonsense Rb1 mutations and do not express retinoblastoma protein (Rb). Therefore Rb expression in cells within these tumors indicates a cell that was not derived from the malignant clone. Expression of Rb and other proteins was determined using immunocytochemistry in tumors obtained from enucleated eyes of children with retinoblastoma or of cell cultures derived from these tumors. Cultures of tumor cells were grown either in defined serum-free or serum-supplemented media.

Results
Retinoblastoma tumors contain a small percentage of cells that are Rb positive but are morphologically indistinguishable from the Rb negative cells within the tumor. The Rb positive cells are seen in greater number adjacent to the retina. Similar to the Rb negative cells, some of the Rb positive cells express proteins associated with neural stem cells (CD133, nestin, sox2) while other Rb positive cells express proteins associated with differentiated neural cells (GFAP, NSE, synaptophysin). Tumors cells grown in defined medium form neurospheres that do not express Rb but do express stem cell and differentiation markers similar to the primary tumor. Tumor cells grown in serum-containing medium are heterogeneous for the expression of Rb.

Conclusion
Both Rb expressing and non-expressing cells can grow in tissue culture but only Rb negative cells form neurospheres. Retinoblastoma tumors appear to contain both cells of malignant and non-malignant origin that only can be distinguished by their expression of Rb.

Origin of human retinoblastoma: using the SD-OCT to determine the retinal layer of origin

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Background
The cell of retinoblastoma origin based cell markers is unclear. Interphotoreceptor retinoid-binding protein and cone specific genes were found to be frequently expressed suggesting that photoreceptors are the most likely candidates. The classic Flexner-Wintersteiner rosettes seem to mimic photoreceptor differentiation. However, markers of other cell types are found in retinoblastoma tumors, including Müller glia, amacrine, and ganglion cells. Optical coherence tomography (OCT) can visualize individual retinal layers to address this problem.

Methods
We retrospectively reviewed images of small retinoblastoma tumors obtained with the hand-held SD-OCT (Bioptigen, Inc., Research Triangle Park, Durham, North Carolina) to determine the retinal layer of origin of the tumors.

Results
A newborn child carrying the RB1 mutant alleles of his bilaterally affected parent, had a macular tumor in each eye (IIRC Groups B/B; TNM: T1b N0 M0). The SD-OCT image of the smaller tumor showed that the tumor lay within the inner nuclear layer of the retina. A 5 month-old baby with no family history of retinoblastoma had multiple tumors in the right eye with no seeding and minimal sub-retinal fluid surrounding the tumor masses (IIRC Grade B). The left eye had a massive tumor with extensive seeding (IIRC Group D; TNM: T2b N0 M0). The child was treated with systemic chemotherapy. The SD-OCT of the smaller tumor in the right eye showed that it arose in the inner nuclear layer.

Conclusion
We hypothesize that the cell of origin of retinoblastoma normally resides within the inner nuclear layer.

Retinoblastoma has properties of a cone precursor tumor

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Background
Retinoblastomas develop due to the loss of Rb, yet the cells in which Rb suppresses retinoblastoma and the circuitry that underlies the need for Rb are undefined. As mouse models do not accurately reproduce human retinoblastoma, we examined whether human retinoblastoma cells have features of a specific retinal cell type, and whether the corresponding normal cells have circuitry that could predispose to retinoblastoma tumorigenesis.

Methods
Retinoblastomas and fetal retinas were examined for expression of retinal markers and oncogenic proteins. shRNAs were used to knockdown signalling proteins that were expressed in normal retinal cells and retinoblastoma tumors. Chromatin immunoprecipitation (ChIP) and luciferase assays were used to assess whether a retinal cell-specific factor (RXRγ) regulates an oncogenic signalling protein (MDM2) in retinoblastoma cells.

Results
Retinoblastoma cells expressed markers of cones, including RXRγ, TRβ2, and L/M opsin. Cells that lacked cone markers expressed Rb and/or retained RB1 alleles and were thus non-neoplastic. Cone-like tumor cells propagated retinoblastoma in serial xenografts. MDM2 and N-Myc were highly expressed in normal human but not mouse cone precursors and were required for retinoblastoma cell proliferation and survival. The human but not mouse MDM2 promoter had an RXRγ recognition element that contributed to promoter activity. The cone-specific RXRγ protein associated with the MDM promoter in ChIP assays, and both RXRγ and TRβ2 were required for retinoblastoma cell proliferation and survival.

Conclusion
Retinoblastoma has properties of a cone precursor tumor and depends upon cone-specific signalling proteins. These findings provide support for a cone precursor origin of retinoblastoma tumors.

Are children born after infertility treatment at increased risk of retinoblastoma?

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Background
Retinoblastoma is the most frequent eye tumour in children, with an incidence of 1 in 15–20,000 births and 11% of all cancers in the first year of life. This disease can be linked to a genetic predisposition but outside familial forms, the causes are not well known. Studies have recently suggested an increased risk of retinoblastoma among children born after in vitro fertilization (IVF). However, little information is available and results are not consistent. We assessed the association between infertility treatments and retinoblastoma.

Methods
We included all infants living in France diagnosed with retinoblastoma between 1 January 2000 and 31 December 2006 by the Institut Curie, a reference centre for both diagnosis and treatment of retinoblastoma. They were compared to a national sample of births in France in 1998 and 2003 (N=28,170), using multiple logistic regression.

Results
243 non-familial cases were included. There was an increasing risk of retinoblastoma with increasing maternal age [Adj OR=1.96 (1.25–3.08) at ≥35, versus <25] but the association with IVF [Adj OR=1.51 (0.70–3.23)] and ovarian stimulation [Adj OR=1.31 (0.73–2.36)] was not statistically significant after adjusting for maternal age, tobacco consumption and level of education.

Conclusion
Our study did not identify a significantly increased risk of retinoblastoma associated with infertility treatments, and in particular IVF.

Higher incidence of retinoblastoma in children born after in vitro fertilization found in the Dutch retinoblastoma register

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Background
In 2003 we already reported in the Lancet about a statistically significantly increased risk of retinoblastoma in children born after in vitro fertilization (IVF) in the Netherlands.

Methods
Now we have performed this cohort study among Dutch retinoblastoma patients over an extended period. By means of a questionnaire, information about fertility treatments from parents of all retinoblastoma patients, diagnosed between 1995–2007, was collected.

Results
A total of 162 retinoblastoma patients were diagnosed between January 1 1995 and December 31 2007. Seven patients (4%) were born after IVF; 3 hereditary and 4 non-hereditary cases. The expected number of retinoblastoma cases among children born after IVF or ICSI was estimated to 2.76 cases (95% CI=2.67–2.84). With 7 observed cases, the RR was 2.54 (95% CI=1.02–5.23). The absolute excess risk on retinoblastoma among children born after IVF was 1.05 per 10,000 person-years.

Conclusion
We found again an increased risk of retinoblastoma in children born after IVF in a population-based study; this finding requires further research to confirm the association and to explore a possible causal mechanism. Caution and awareness on one hand and avoiding unnecessary worries on the other hand are mandatory at this stage of our knowledge.

Anatomic, histopathologic, and gene expression analysis of metastatic tumors in the $LH_{BETA}T_{AG}$ transgenic mouse model of retinoblastoma

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Background
The purpose of this study was to: 1) establish a non-invasive imaging protocol that can be used to document the growth of animal model retinoblastoma, and 2) characterize the metastatic disease that develops in the $LH_{BETA}T_{AG}$ transgenic mouse model.

Methods
Transgenic mice which developed bilateral tumors by 16 weeks of age were evaluated. The anatomic location of the tumors and metastases was explored by performing MRI scans every 4 weeks and comparing abnormally enlarged structures to scans performed on wild type mice. Eyes were enucleated at 20 weeks and metastatic disease sites were followed serially by MRI to confirm disease enlargement over time. Animals were euthanized at 32–40 weeks and metastases were harvested. Histopathologic analysis was performed on both primary tumor and metastatic tissue. Gene expression analysis by microarray was performed by isolating total RNA from the primary tumor and metastatic tissue.

Results
A standard MRI sequence was established which was able to accurately detect small intraocular tumors as well as large ones and track their growth. Metastases were consistently identified by the age of 27 weeks in the parotid and salivary glands and were shown to increase in size with time. Additional less common metastatic sites included the brain, lungs, and liver. Gene expression analysis revealed a consistent difference in the profile of genes expressed in primary tumor versus metastatic disease.

Conclusion
Murine retinoblastoma displays a unique pattern of metastatic disease development with masses forming initially in the parotid and salivary glands. A unique profile of gene expression is present in metastatic sites compared to the primary tumor. These genomic changes present a possible therapeutic target for the treatment of advanced or metastatic human retinoblastoma.

Retinoblastoma tumor burden: effect of macrophage depletion on $LH_{BETA}T_{AG}$ retinal tumor growth

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Background
Macrophages are an integral part of the tumor microenvironment having supporting roles in tumor growth and angiogenesis in 80% of the tumors. The purpose of this study is to analyze the effect of macrophage depletion on $LH_{BETA}T_{AG}$ retinal tumor growth.

Methods
This study was approved by the IACUC and follows ARVO guidelines. Macrophage depletion was performed by subconjuctival delivery of chlodronate-encapsulated liposomes in 10-week-old mice. Animals (n=7) were treated bi-weekly for a total of 6 weeks, and were analyzed at 16 weeks of age. The control group (n=7) received subconjuctival administrations of PBS-encapsulated liposomes. The effective depletion of macrophages was confirmed by flow cytometry of circulating monocytes and immunohistochemistry. Macrophages were detected with F4/80 and M2 polarized macrophages were detected with CD-163.

Results
There was a significant decrease of macrophages in the group treated with chlodronate-encapsulated liposomes ($p=0.0366$). Following macrophage depletion, tumor burden increased ($p=0.0564$), the expression levels of the gelatinase matrix metalloproteinase-9 decreased ($p=0.0142$), and the density of the tumor promoting M2 polarized macrophage did not change ($p=0.680$).

Conclusion
In the present study we show that the density of M2 polarized tumor promoting macrophages remains stable and, due to the significant decrease of total macrophages density, it is possible that the remaining macrophage population is M1 polarized. Consistent with previous studies, the depletion of the M1 polarized macrophages would result in tumor growth, since the M1 population releases cytotoxic activity on tumor cells unchaining tissue destructive reactions centered on the vascular endothelium.

Comparison of the protein profile in human retinoblastoma tumor and seeding

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Purpose
To compare the pattern of protein expression of retinoblastoma tumors and seedlings.

Methods
Five retinoblastoma tumors and seven seedlings were studied. The tissues were subjected to high-resolution two-dimensional gel electrophoresis. Silver staining developed the individual protein spots. The protein expression profiles were compared in the retinoblastoma tumor group and in the seeding group and between them.

Results
The overall protein expression profiles within the retinoblastoma tumor group were quite similar and so were the profiles in the seeding group. Significant differences in the protein pattern between the two groups were seen.

Conclusion
Remarkable consistency of the protein expression patterns was found within the retinoblastoma group and within the seeding group, but significant differences between the groups were present. Identification of individual protein differences could provide further insight into the pathophysiology of the seeding process.

TGF-β1, TGF-β TYPE 2 receptor, survivin and HLA Class II expressions in retinoblastoma

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Background
The expression patterns of TGF-β1, TGF-β type 2 receptor, survivin and HLA class II were investigated in retinoblastoma and their correlations with clinicopathological parameters were assessed.

Methods
Pathologic specimens of 60 enucleated eyes were used to construct microarrays. Tumor differentiation, anterior chamber invasion, choroidal invasion, scleral invasion, extraocular extension, post-laminar optic nerve involvement, necrosis, relapses, tumor height and preoperative treatment status were noted for each eye. Immunohistochemical techniques were used to study the tissue microarrays for the expression of the TGF-β1, TGF-β type 2 receptor, survivin, HLA class II. Fisher exact test was used for two group analysis and multiple comparisons were performed for correction between subgroups.

Results
Thirty-six tumors were well-differentiated and 24 tumors were poorly differentiated. Increased expression of TGF-β1 ($p=0.001$) and survivin ($p=0.0003$) expressions were noted in aggressive tumors. TGF-β1 expression was also increased in large tumors (tumor height >14mm). TGF-β type 2 receptor expression was decreased in aggressive ($p=.00$), high grade ($p=0.009$) and larger tumors ($p=0.001$). Metastatic disease was detected in 11 patients. Negative TGF-β type 2 receptor expression was found to be relevant to metastasis. Tumor tissues did not stain with HLA class II, whereas antigen presenting cells showed strong expression.

Conclusion
Retinoblastoma may use immune escape mechanisms such as secreting immune suppressive factors like TGF-β1 and alterations may occur in TGF-β type 2 receptor to protect tumor itself from inhibitory effects of TGF-β and resist to apoptosis by expressing survivin.

The miR-17-92 gene is amplified and over expressed in retinoblastoma

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Background
MicroRNAs are small non-coding RNAs that regulate gene expression. They play important roles in diverse biological processes, including development, cell proliferation, differentiation and apoptosis. Aberrant microRNA expression is involved in pathogenesis and progression of human malignancies, including embryonic tumours. Retinoblastoma is the most common eye tumour of childhood, and is mainly driven by mutations in the Rb1 gene. Genomic alterations including amplification of chromosome 6p22 have been identified in retinoblastomas, but neither high-resolution CGH nor microRNA expression has been investigated to date.

Methods
We used high-throughput, real-time PCR to analyse the expression of 430 microRNAs in retinoblastomas in comparison to normal human retina. In addition, array CGH was employed to analyse gene copy number alterations in the same tumour cohort.

Results
Among other microRNAs aberrantly expressed, the oncogenic miR-17-92 cluster was strongly expressed in retinoblastomas. In addition, the gene encoding the miR-17-92 primary transcript was amplified or a gain of the respective genomic region was observed in a subset of retinoblastomas. Transfection of antagomirs (modified antisense micro-RNAs) into established RB cell lines also led to a significant decrease in cell growth.

Conclusion
The oncogenic miR-17-92 cluster could be targeted as a novel treatment strategy for retinoblastoma using antagomirs.

RB1-mutations, second primary malignancies and hereditary retinoblastoma

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Background
The risk of second primary malignancies in hereditary retinoblastoma subjects has been examined in many studies, but no study has been done on a possible relation between specific RB1-germline mutations and the risk of second primary malignancies in a nationwide well-documented cohort.

Methods
Extensive follow-up procedures of hereditary retinoblastoma subjects of the Dutch retinoblastoma cohort (1862–2005) were conducted during the period of September 2005 to June 2007. Hereditary retinoblastoma subjects with and without a second primary malignancy were genotyped for mutations in RB1. Risks of second primary malignancy incidence among hereditary retinoblastoma subjects with specific documented RB1-mutations were examined and compared on the basis of patient characteristics.

Results
Of the 199 hereditary retinoblastoma subjects with a known RB1-mutation, 44 developed a second primary malignancy after a median follow-up of 30.2 years (range 1.33–76.0). Risk was significantly associated with radiotherapy for retinoblastoma (hazard ratio, 3.94; [95% confidence interval, 1.73–8.98]; $P<.001$), and there was a trend toward higher second primary malignancy risk for hereditary retinoblastoma subjects with a nonsense or frameshift mutation vs. other RB1-mutations (hazard ratio, 1.58; [95% confidence interval, 0.82–3.07]; $P=.17$).

Conclusion
Although no statistically significant genotype-phenotype correlations emerged between hereditary retinoblastoma subjects with a documented RB1-mutation and second malignancies, we observed a trend towards higher second primary malignancy risk for hereditary retinoblastoma subjects with a nonsense or frameshift mutation compared to other RB1-mutation.

Role of linkage analysis in excluding risk for siblings and cousins in familial retinoblastoma

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Background
A small proportion of retinoblastoma cases with no known family history and uninformative genetics (both unilateral and bilateral) will have been inherited. Empiric risk to siblings of these apparently de-novo cases is around 6% and 1.6% for bilateral and unilateral cases respectively.

As the risk to relatives of apparently de-novo cases is low (<5%), and surveillance often involves repeated anaesthesia, mutation studies help exclude risk and avoid unnecessary examinations. However these are informative, at best, in around 90% of cases. Linkage exclusion is an alternative, sometimes underused approach, involving use of linked polymorphisms on chromosome 13 to determine risk where mutation testing has been uninformative.

Methods
20 families with an index case of retinoblastoma and uninformative genetic analysis were included in the study. Over 100 at risk relatives were identified and linkage analysis performed in the nuclear family.

Results
We were able to use this technique in a proportion of siblings, (and cousins where we were approached by the referring ophthalmologist or parents) to exclude risk. Linkage analysis is informative in 25% of full siblings, 50% of half siblings and 75% of cousins. The utility increased, the more distant the relative and would advocate proactive use for siblings and a low threshold for a reactive approach in more distant relatives.

Conclusion
There is no consensus on surveillance of cousins, and linkage analysis is particularly useful in excluding risk in many such low risk cases, avoiding anxiety and inconvenience to the families, and reducing the burden on healthcare services.

The uptake of prenatal testing for retinoblastoma susceptibility by pregnant women at increased risk

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Background
Prenatal diagnosis (PND) is offered to all women at risk of having offspring with hereditary retinoblastoma, based on a previously identified germline mutation of the RB1-gene. Couples have the option to terminate the pregnancy, if the foetus tests positive. The objective of this study was to evaluate the nationwide uptake and outcome of PND for this cancer susceptibility.

Methods
We scored the total number of families with a known germline mutation of the RB1-gene and of requests for PND. Follow-up data were obtained by reviewing medical files. We compared the uptake of PND for RB susceptibility with other hereditary high risk cancer susceptibility syndromes.

Results
We identified 161 families with a known RB1-mutation in the Netherlands. PND was performed 30 times for 20 families (12%). Half of the couples had a recurrence risk of 50% and the other half a recurrence risk of 2–3%, based on possible germline mosaicism. Eleven foetuses tested positive; 8 pregnancies were terminated.

Of the 260 nationwide registered families with familial adenomatous polyposis with a germline mutation of the APC-gene, 6 (2%) performed PND. Likewise, in less than 0.5% of >2000 nationwide registered BRCA1/BRCA2-mutation positive families, PND was performed, and in one of 48 nationwide registered families with Von Hippel Lindau syndrome (2%).

Conclusion
Hereditary retinoblastoma has an impact on reproductive decisions, PND and pregnancy termination. Compared to other hereditary cancer syndromes, prenatal diagnosis seems to be performed substantially more often for retinoblastoma susceptibility. Reasons for differences will be discussed.

Combined hamartoma of the retina and retinal pigment epithelium in 77 consecutive patients

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Purpose
To evaluate clinical characteristics and visual outcomes.

Method
Retrospective review.

Results
Of 77 patients, the mean age at presentation was 12 years. The majority were Caucasian (91%) and male (68%). Referring diagnosis was correct in 25% of cases. Incorrect diagnosis included melanoma (8%), nevus (6%) and retinoblastoma (5%). The most common presenting symptom was decreased visual acuity (32%). The mean tumor thickness was 2mm and base 8mm. The visual acuity decreased from initial visit (macular tumor 20/320, extramacular tumor 20/80) to 10-year follow-up (macular tumor 20/2000, extramacular tumor 20/100).

Conclusion
Combined hamartoma is often misdiagnosed. Progressive visual loss is common, particularly with macular tumors.

Focal pseudoneoplastic retinal gliosis: a new clinical entity?

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Background and objective
To report a small series of patients each of whom had a solitary retinal lesion that we have called focal pseudoneoplastic retinal gliosis (FPNRG) and to describe how it differs from other known retinal lesions.

Methods
Seven patients were identified each of whom had an asymptomatic, superficial, yellow-white retinal lesion that did not meet diagnostic criteria for astrocytic hamartoma (AH), retinoblastoma (RB), or other known lesions. Their charts were reviewed to determine systemic disease, personal or family history of tuberous sclerosis complex (TSC), age at diagnosis, gender, and visual acuities. The ophthalmoscopic features, including calcification, retinal traction, and findings on fluorescein angiography, ultrasonography and optical coherence tomography.

Results
There were 5 men and 2 women with a mean age of 60 years (median 53; range 43–85). All lesions occupied the inner retina, were abruptly elevated, opaque, and yellow-white in color. Unlike the typical AH of TSC, they were diagnosed in older individuals, totally obscured the underlying retinal vessels, produced no traction, lacked calcification, and had no association with TSC. OCT showed an abruptly elevated lesion that originated from the inner retina. One lesion spontaneously disappeared.

Conclusion
FPNRG appears to be newly recognized entity that most closely resembles AH and RB but it is diagnosed in older adults without TSC and has features that help to differentiate it from those well-known lesions. Focal pseudoneoplastic retinal gliosis should be included in the differential diagnosis of small non-pigmented retinal lesions.

Friday
11th September 2009

Retinal tumours

Session 5

Retinal tumour case reports

Friday
11th September 2009

Retinal tumours

Posters

Simultaneous ocular toxoplasmosis, toxocarosis and retinoblastoma in the same eye of a 4-year-old girl

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Background
In opaque media, presumed hypertensive uveitis with no vitreal calcifications, positive serology and resistance to treatment in a child more than 4-year-old, presents a diagnostic challenge that may only be resolved by histopathologic findings.

Case report
A young girl aged 4 years and 4 months presented with a painful RE associated with leukocoria. She lived on a farm with numerous dogs and cats. Ocular examination under general anaesthesia revealed ocular hypertension, a greyish vitreous opacity and no fundus visibility. Ultrasonography showed diffuse vitreal hyper-reflectivity with no tumoral mass and no calcifications. Serologic investigation was positive for toxoplasmosis and toxocarosis. Despite anti-parasitic treatment a pseudo-hypopyon and calcifications developed. Enucleation was advised but the parents refused, preferring to consult a faith healer. Buphthalmos and scleral ectasia followed, evolving 5 months later into painful phthisis bulbi. The parents finally consented to enucleation. Histopathology was consistent with Rb with retrolaminar optic nerve invasion as well as massive choroidal, scleral and orbital involvement. Orbital radiotherapy, adjuvant chemotherapy and stem cell re-infusion was given. 4 years after the end of treatment the child is disease-free.

Conclusion
The association of retinoblastoma with another ocular disease or malformation is rare and may result in an atypical clinical course, thus delaying diagnosis. In children, enucleation has to be considered in cases with atypical semiology and unsatisfactory response to treatment if retinoblastoma cannot be excluded.

Iodine-125 (I-125) brachytherapy an alternative to enucleation or external beam radiation (EBR) in papillary retinoblastoma

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Background
After first-line treatment, any papillary contact of residual tumor is life-threatening and requires either enucleation or EBR (preferably with a conformal stereotactic technique).

Patients and methods
3 infants with Rb (2 unilateral, 1 bilateral) diagnosed at 3, 14 and 5 months respectively, underwent chemotherapy and chemothermotherapy. In 2 cases the macular tumor recurrence invaded the papillary and/or peripapillary area, defined as the projection of the retrobulbar optic nerve diameter. In the third case, the tumor regressed (type I) but contact with optic nerve head persisted. 10mm notched or 12mm diameter I-125 plaques were used (customized COMS plaques).

Results
In the two macular cases total regression was observed 1 month after brachytherapy. One infant developed actinic retinopathy 7 months later. In the third case, the calcified papillary tumor remained unchanged but radiation-induced papillitis developed 5 months later. No recurrence occurred at respectively 1½, 3½ and 4 years' follow-up.

Conclusion
The lateral dosimetry characteristic of I-125 brachytherapy, contrary to that of 106 Ruthenium, allows irradiation of adjacent tissue such as the optic disc and thus offers an alternative to enucleation or EBR in cases with residual or recurrent papillary tumor located in the eye with the least good visual prognosis.

Saturday
12th September 2009

Intraocular lymphoma and TNM

Session 1

Intraocular lymphoma in Japan

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Objective
To clarify the clinical profile of patients with intraocular lymphoma (IOL) in Japan.

Methods
246 cases with IOL were enrolled in this study from 25 institutes. This retrospective study was based on review of clinical charts. The mean follow-up period was 41.3 (2–161) months.

Results
The male/female ratio was 1:1.5. The mean age at the time of diagnosis was 63.7 (35–90) years. Two-thirds of the patients had bilateral IOL. Ocular symptoms included blurred vision (48%), decreased visual acuity (25%), and floaters (22.0%). Ophthalmological examination detected vitreous opacity in 89% and subretinal infiltrates in 57%. Central nervous system (CNS) involvement was observed in 54%, intraocular lesion alone in 25%, and both CNS and systemic lymphoma in 10%. Intraocular lymphoma occurred as primary lymphoma in 73%, ocular relapse of CNS lymphoma in 14%, and CNS relapse of systemic lymphoma in 12%. The average period from ocular manifestations to CNS symptoms was 22 months, whereas the average period from CNS symptoms to ocular manifestations was 13 months. From the examination of vitreous biopsies, a positive result was obtained by cytology in 48%, by cytokine analysis (IL-10/IL-6>1) in 91%, and by IgJH gene rearrangement in 81%. All three examinations were positive in 22% of the patients. Thirteen months was required for the diagnosis of primary IOL, whereas primary CNS lymphoma was diagnosed 5 months after the initial symptoms.

Conclusion
The clinical profile of IOL in Japanese patients was defined by the multicenter survey. Outcome analysis is being conducted on this series.

PIOL: local or systemic therapy?

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Purpose
To review recent studies from our group which have looked at the epidemiology of primary CNS lymphoma (PCNSL), the course of primary intraocular lymphoma (PIOL) after local and systemic therapy and the initial studies on the use of intraocular rituximab.

Method
Review of results of four peer-reviewed journal articles.

Results
There is a statistically significant difference in the incidence of PCNSL in whites compared with blacks in the less than 50 age group and the greater than 50 age group. The median time to relapse for PIOL is 19 months. Median progression free (PFS) and overall survival (OS) were 29.6 and 58 months, respectively, and unaffected by local or systemic therapy or treatment type. Finally, rituximab appears to penetrate all layers of retina and appears to have limited toxicity in animal studies and in a few humans.

Conclusion
Since patients are living longer and toxicity of present local and systemic therapy is being seen, consideration to local therapy with intravitreal methotrexate in combination with rituximab or rituximab alone should be given.

American Joint Committee on Cancer TNM classification for lacrimal-gland adenoid cystic carcinoma is predictive of outcome

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Purpose
To investigate whether the American Joint Committee on Cancer (AJCC) classification at initial diagnosis of lacrimal gland adenoid cystic carcinoma predicts outcome and to evaluate the impact of treatment on local recurrence.

Patients and methods
Consecutive patients with adenoid cystic carcinoma of the lacrimal gland treated at 8 institutions between January 1986 and December 2007. The clinical records, including pathology reports and imaging studies, were reviewed.

The AJCC TNM classification, histologic subtype, local recurrence rate, and survival were studied in each case.

Results
AJCC classification at initial diagnosis was assessable for 53 patients and was as follows: T1N0M0, 7 patients; T2N0M0, 8; T3aN0M0, 14; T3aNxM0, 1; T3aN0M1, 1; T3bN0M0, 13; T3bN0M1, 1; T4aN0M0, 2; T4bN0M0, 4; T4bN0M1, 1; and T4bNXM0, 1. 38 (72%) of the 53 patients had >T3 tumors at presentation. Of the 38 patients with >T3 tumors, 20 were treated with orbital exenteration and postoperative adjuvant radiotherapy (RT); 6 were treated with orbital exenteration without RT; and 12 were treated with globe-preserving surgery (10 with RT and 2 without). Of the 15 patients with <T3 tumors, 6 were treated with globe-preserving surgery and RT, 2 were treated with globe-preserving surgery without RT, 6 were treated with orbital exenteration with bone removal and RT, and 1 was treated with orbital exenteration with bone removal

without RT. This last patient was the only patient with a <T3 tumor who had local recurrence. Among patients with >T3 tumors, the risk of local recurrence (in the orbit or skull base) was higher in patients treated with conservative surgery as opposed to orbital exenteration and RT. Only 4 (20%) of the 20 patients treated with orbital exenteration and RT had local recurrence, compared to 3 of 6 (50%) of the patients treated with orbital exenteration without RT and 8 (67%) of the 12 patients treated with globe-preserving surgery. Overall, 17 (45%) of the 38 patients with >T3 tumors and only 1 (7%) of the 15 patients with <T3 tumors died of disease during the study period.

Conclusion

In patients with lacrimal-gland adenoid cystic carcinoma, AJCC >T3 at initial diagnosis correlates with worse outcomes than does AJCC <T3.

A TNM-based clinical staging system of ocular adnexal lymphomas

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Background
The ocular adnexal lymphomas (OAL) arise in the conjunctiva, orbit, lacrimal gland and eyelids. To date, they have been clinically staged using the Ann Arbor staging system, first designed for Hodgkin- and later for nodal non-Hodgkin lymphoma (NHL). The Ann Arbor system has several shortcomings, particularly when staging extranodal NHLs, such as OAL, which show different dissemination patterns from nodal lymphomas.

Objective
To describe the first tumor, node and metastasis (TNM)-based clinical staging system of OAL.

Results
We have developed the first American Joint Committee on Cancer - International Union Against Cancer (AJCC-UICC) TNM-based staging system for OAL to overcome the limitations of the Ann Arbor system. Our staging system defines disease extent more precisely within the various anatomical compartments of the ocular adnexa, and allows for analysis of site-specific factors not addressed previously. It aims to facilitate future studies by identifying clinical and histomorphological features of prognostic significance. This system is for **primary** OAL only, and is **not** intended for intraocular lymphomas.

Conclusion
Our TNM-based staging system for OAL is a user-friendly anatomic documentation of disease extent, which creates a common language for multi-centre and international collaboration. Data points will be collected, with the aim to identify biomarkers, to be incorporated into the staging system.

An eye cancer bio-informatics grid initiative of the AJCC-UICC Ophthalmic Oncology Task Force

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Background
An eye cancer bio-informatics grid will enable clinical and research centers to work together. Cooperation is crucial because eye cancers are rare. Individual centers do not have enough patients to determine the best methods for diagnosis and treatment. Standardized data from thousands of patients must be pooled to achieve statistical significance and find critical answers in our lifetime.

Methods
Forty-five eye cancer specialists, from 10 countries, have developed a common language to define (stage) eye cancers, in the form of the 7th edition of the TNM staging system. The Ophthalmic Oncology Task Force of the AJCC included members various committees and societies, for example, the UICC, ISOO, ARVO, AAO, ASTRO, AAPM, CAP, EORTC and ASOPRS. The staging system was written to encourage and enable multi-center, international, cooperative research.

Results
EyeCaBIG (http://eyecancerbig.org) required staging systems for cancers of the eyelid, conjunctiva, uvea, retina, orbit (sarcomas/lacrimal gland) and ocular adnexal lymphomas as a foundation for communication. Related projects were commenced following the finalisation of the chapters: for example, Kivela and Singh are organizing the requirement of the TNM staging in "instructions for authors" in lead ophthalmic journals. Grossniklaus, Edward, Ainbinder and Coupland lead an effort to develop an online, open-access, web-based, high-definition pathology teaching tools for each staging system. Gallie, Simpson and Damato are leading efforts to develop EMR-based data collection that will form the core of our EMR2Database initiative. A model system is currently deployed for retinoblastoma (Canada, Kenya and India) and a second is under construction for uveal melanoma. Each does, or will, incorporate a 7th Edition AJCC-UICC Staging System.

Conclusion
EyeCaBIG has provided a window opportunity to collect a variety of data related to eye cancers. However, its support, development and implementation will require broad participation. The implementation of bio-informatics can lead to better understanding of the histogenesis of these tumours, an improvements in their treatments and, possibly, save lives.

Saturday
12th September 2009

Intraocular lymphoma, and TNM staging

Posters

A case of intra- and extraocular extranodal marginal zone B cell lymphoma of the mucosa-associated lymphoid tissue type (MZBCL)

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Background
Extranodal marginal zone B cell lymphoma of the mucosa-associated lymphoid tissue type (MZBCL) rarely invades the intraocular tissue.

Methods
A retrospective case report, focusing on the clinical, radiological, and histopathological findings of a 49-year-old male patient.

Results
Ophthalmic examination revealed serous retinal detachment OD. Ultrasonography depicted choroidal and extrascleral low-echoic lesion behind the retinal detachment. Magnetic resonance imaging also showed the intra- and extraocular lesion spreading along the optic nerve OD and the bone marrow invasion to the sphenoid. Positron emission tomography (PET)–CT and gastric endoscopy did not detect any other systemic invasion. Biopsy of the extraocular tissue, including the Inferior oblique muscle, was performed, and histopathological diagnosis was MZBCL.

Conclusion
Orbital MZBCL is typically indolent and localized tumor, but may invade the choroid. The concomitant extraocular lesion can be an important clue for diagnosis and the following treatment.

Application of microvesicle contrast enhanced ultrasonography in the differential diagnosis of intraocular tumors

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Objective
To investigate the value of microvesicle contrast enhanced ultrasonography in the diagnosis and differentiation of intraocular tumors.

Method
Eighty cases that were diagnosed clinically with intraocular tumors underwent contrast enhanced ultrasound examinations. SonoVue was chosen as the contrast agent in this study. Various manifestations of these intraocular masses in the contrast ultrasonic imaging were observed and recorded for further comparison. Special attention was paid to the features of contrast agent visualization in tumor masses and other confounding lesions that needed differentiation.

Results
All intraocular tumors demonstrated visualization of contrast agent inside the masses. The visualization and filling of contrast agent were of varying degrees and durations in tumors of different types. Other pathologic changes for differentiation such as subretinal hemorrhage and age-related macular degeneration did not show visualization of contrast agent inside the lesions of interest while filling of contrast agent could be observed in the retina above these lesions.

Conclusion
Microvesicle contrast enhanced ultrasonography can differentiate between intraocular masses and other confounding non-mass pathologic changes. The ultrasonic characteristics of intraocular masses still need further analysis and summarization.

Biological effects of VEGF *in vitro* and *in vivo* as a rationale for anti-VEGF therapy

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Background
VEGF is a multifunctional cytokine that induces physiological vascularization and tumor angiogenesis. The survival of activated endothelial cells (EC) and newly generated tumor microvessels depends on VEGF. Hence, inhibition of angiogenesis using anti-VEGF therapy is a promising trend in modern ophthalmooncology.

Aim
To investigate VEGF biological effects *in vitro* and *in vivo* as a rationale for anti-VEGF therapy terms.

Materials and methods
The effects of VEGF on cell proliferation (cultivated SVEC-4-10 murine ECs transformed by SV40), migration (modified method of "wound surface") and tubule-like structures generation in Matrigel were studied.

Results
VEGF increased EC proliferation and migration in a dose-dependent manner. VEGF level of 10 ng/ml resulted in 130±12% ECs augmentation while its level of 50 ng/ml produced 160±27% ECs augmentation as against control. On the contrary, 10 ng/ml bFGF increased this parameter by 122% as against negative control. VEGF promoted angiogenesis in Matrigel. Significant differences between the groups were revealed when VEGF level was 400 ng/ml. Peak angiogenesis was observed at 800 ng/ml VEGF.

Conclusion
VEGF biological effects strongly correlate with its concentration. ECs activation, proliferation and migration are detected at 10–50 ng/ml VEGF while tubule-like structures can be generated only at 400 ng/ml VEGF. The suppression of this peptide using anti-VEGF therapy requires treatment doses escalation in the course of angiogenesis transformation from ECs migration to microvessel generation as well.

Video indirect ophthalmoscope – home made

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Background
Documentation of fundus findings on initial and follow-up examination in infants and children with fundus diseases such as retinoblastoma is particularly essential. Fundus photography in adults is possible with a fundus camera or with a portable video camera during slit lamp fundus biomicroscopy for posterior pole photography or video recording. However, fundus photography is usually impossible in infants and young children while awake or under anesthesia and expensive equipment such as the RetCam is usually necessary, the less expensive option being the video indirect ophthalmoscope.

Methods
Hand-held digital video camera was modified using an innovative home-made device to create a digital video indirect ophthalmoscope. This device was used to document findings in children with retinoblastoma being examined under general anaesthesia and adult patients with intraocular mass lesions.

Results
Still fundus photographs and videos of reasonable quality could be obtained using the device. Scleral depression is not possible with this technique, the other limitation being a learning curve before using the device.

Conclusion
Hand-held digital video camera can be modified to be used as a video indirect ophthalmoscope that can be used to document fundus findings in children with retinoblastoma examined under general anaesthesia. This could be a cost-effective option particularly in developing countries.

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